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Therapeutic Class Review
HMG-CoA Reductase Inhibitors (Statins)
Single Entity Agents

I. Overview

The single entity hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly referred to as "statins") include atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. All agents are formulated for oral administration, with lovastatin and fluvastatin available as sustained-release tablet formulations. Lovastatin, pravastatin, and simvastatin are available generically. Statins work by inhibiting HMG-CoA reductase.[1] HMG-CoA reductase is the rate-limiting enzyme in hepatic cholesterol synthesis, which catalyzes the conversion of HMG-CoA to mevalonate, a cholesterol precursor. Reduced hepatic cholesterol synthesis leads to the up-regulation of hepatic low-density lipoprotein cholesterol (LDL-C) receptors and subsequently a decreased production and an enhanced clearance of circulating LDL-C. In addition, HMG-CoA reductase inhibition leads to a reduction in total cholesterol (TC), apolipoprotein B (apo B), triglycerides (TG), as well as an increase in apolipoprotein A (apo A) and high-density lipoprotein cholesterol (HDL-C). The mechanism by which statins increase HDL-C is not fully determined.[1,2]

The single entity statins are all Food and Drug Administration (FDA) approved for the treatment of primary hyperlipidemia, and, with the exception of rosuvastatin, for primary and secondary prevention of cardiovascular events in high-risk patients.[1,2] The agents in this class have demonstrated a significant benefit in reducing TC, LDL-C, and modestly increasing HDL-C. In addition, statins have been shown to reduce the risk of cardiovascular mortality, morbidity (ie, strokes, myocardial infarctions [MIs], congestive heart failure [CHF], major vascular events), and all-cause mortality among patients with and without a prior history of coronary heart disease (CHD). Individual statins differ in their potency, pharmacokinetic parameters, drug-drug interactions, and side-effect profile. All statins may cause an elevation in liver enzymes and creatine kinase, sometimes accompanied by myopathy and rarely rhabdomyolysis and renal failure. Consequently, liver function tests should be performed routinely with statin therapy.

CHD is the leading cause of death in the United States (US).[3] In 2008, 1,200,000 Americans are expected to experience either a new or a recurrent MI, associated with an up to 38% mortality rate.[3] Despite an increased awareness of benefits associated with statin therapy, less than 50% of eligible patients actually receive one. Since CHD is a significant contributor to morbidity and mortality, it is important to identify and treat patients at risk.. The HMG-CoA reductase inhibitors have demonstrated significant improvements in overall mortality in primary and secondary prevention of cardiovascular diseases.

The single entity HMG-CoA reductase inhibitors that are included in this review are listed in Table 1.

Table 1. Single Entity HMG-CoA Reductase Inhibitors Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)
atorvastatin	tablet	Lipitor®
fluvastatin	capsule, sustained-release tablet	Lescol®, Lescol XL®
lovastatin	sustained-release tablet, tablets	Altoprev®, Mevacor®*
pravastatin	tablet	Pravachol®*
rosuvastatin	tablet	Crestor®
simvastatin	tablet	Zocor®*

*Generic is available in at least one dosage form or strength.

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All statins lower cholesterol levels. However, the degree to which individual agents lower cholesterol levels vary. The lipid-lowering effects with single entity statins are noted in Table 2.

Table 2. Effects of the Single Entity HMG-CoA Reductase Inhibitors on Cholesterol and Triglyceride Levels[4-10] *

Statin	Daily Dosage (mg)	TC ↓ (%)	LDL-C ↓ (%)	TG ↓ (%)	HDL-C ↑ (%)
Atorvastatin	10-80	25-58	26.5-60	17-53	5-14
Fluvastatin IR/fluvastatin SR	20-80 IR; 80 SR	17-27 IR; 25 SR	22-36 IR; 35 SR	12-18 IR; 19 SR	3-6 IR; 7 SR
Lovastatin IR/lovastatin SR	10-80 IR; 10-60 SR	16-34; 17.9-29.2 SR	21-42; 23.8-40.8 SR	6-27; 9.9-25.1 SR	2-9.5; 7.4-13.1 SR
Pravastatin	10-80	16-33	22-41	6-24	2-12
Rosuvastatin	5-40	24-46	28-63	10-43	3-22
Simvastatin	5-80	19-52	26-47	8-41	7-16

IR=immediate release, SR=sustained release, TC=Total Cholesterol, LDL-C=Low-density Lipoprotein Cholesterol, TG=Triglycerides, HDL-C=High-density Lipoprotein Cholesterol
*The data presented in the table above are pooled from different studies incorporating various indications and may not be directly comparable.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the single entity HMG-CoA reductase inhibitors (statins) are summarized in Table 3. For a comprehensive overview of the treatment of dyslipidemia, please refer to the Appendix.

Table 3. Treatment Guidelines Using the Combination HMG-CoA Reductase Inhibitors

Clinical Guideline	Recommendation
National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)[11]**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low-density lipoprotein cholesterol (LDL-C)-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate-risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (eg, bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (eg, ≥160 mg/dL), the dose of statin may have to be increased or a second agent (eg, a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. For the treatment of heterozygous familial hypercholesterolemia (FH) • Begin LDL-C-lowering drugs in young adulthood. • TLC indicated for all persons. • Statins: first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple-drug therapy (statins and bile acid sequestrants and nicotinic acid). For the treatment of homozygous FH • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia).

Clinical Guideline	Recommendation
	For the treatment of familial defective apolipoprotein B-100 (FDB) • TLC indicated. • All LDL-C-lowering drugs are effective. • Combined drug therapy required less often than in heterozygous FH. For the treatment of polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C-lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP). **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002)**[12]	General Recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. NCEP ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein (LDL)-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Statins • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.
American Heart Association (AHA)/ American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)**[13]	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non–high-density lipoprotein cholesterol (HDL-C) include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy).
Institute for Clinical Systems Improvement (ICSI): **Healthcare Guideline: Lipid Management in Adults (2007)**[14]	• For monotherapy, statins are the drugs of choice for lowering LDL. • If a patient is intolerant to a statin, other statins should be tried before ruling them all out. • If patients are unable to take statins, then bile acid sequestrants, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it. • Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile cid sequestrant, with fewer side effects. • In very resistant cases, triple therapy may be needed.
American Heart	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-

Clinical Guideline	Recommendation
Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart Association (2007)**[15]	line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies (2007)**[16]	• Statins are considered first-line drugs for lowering LDL-C. • When TG are between ~450-900 mg/dL, statins (or fibrates) may be considered as first-choice drugs. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.

III. Indications

Food and Drug Administration (FDA)-approved indications for the single entity HMG-CoA reductase inhibitors (statins) are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials. All product information for the statins stresses that, as recommended by the NCEP ATP III guidelines, therapy with lipid-altering agents should be used in conjunction with a diet restricted in saturated fat and cholesterol for the reduction of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia.[1,2, 4-10] The effects of rosuvastatin on cardiovascular morbidity/mortality end points have not been established.[9]

Table 4. FDA-Approved Indications for the Single Entity HMG-CoA Reductase Inhibitors[4-10]

Indication	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Prevention of Cardiovascular Disease						
Primary prevention of cardiovascular events (patients without clinically evident coronary heart disease (CHD); to reduce the risk of:	✔ *†		✔	✔ §		✔ ‖
Angina	✔ *		✔ ‡ (Unstable)			
Mortality				✔ § (Cardiovascular)	Effect not determined¶	✔ ‖ (CHD death)
Myocardial infarction	✔ *†		✔ ‡	✔ §		✔ ‖ (Nonfatal MI)
Revascularization procedures	✔ *		✔ ‡ (Coronary)	✔ § (Myocardial)		✔ ‖ (Coronary and noncoronary)
Stroke	✔ *†					✔ ‖
Secondary prevention of cardiovascular events (patients with clinically evident CHD); to reduce the risk of:	✔	✔		✔		✔ ‖
Angina	✔					
Hospitalization for congestive heart failure	✔					
Mortality				✔ (Coronary death)	Effect not determined¶	✔ ‖ (CHD death)
Myocardial infarction	✔ (Nonfatal MI)			✔		✔ ‖ (Nonfatal MI)
Revascularization procedures	✔	✔ (Coronary)		✔ (Myocardial)		✔ ‖ (Coronary and noncoronary)
Stroke	✔ (Fatal and nonfatal)			✔ (Stroke and TIA)		✔ ‖

Indication	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Coronary atherosclerosis, slowing its progression in patients with CHD, as part of a treatment strategy to lower total and LDL-C to target levels		✔	✔	✔	✔ #	
Treatment of Dyslipidemias						
Primary hypercholesterolemia (heterozygous familial and nonfamilial; Fredrickson Type IIa) and mixed dyslipidemia (Fredrickson Type IIb)	✔ #	✔ #	✔ #	✔ #	✔ #	✔
To reduce:						
TC	✔	✔	✔	✔	✔	✔
LDL-C	✔	✔	✔	✔	✔	✔
Apolipoprotein B (Apo B)	✔	✔		✔	✔	✔
Triglyceride (TG)	✔	✔		✔	✔	✔
Non–high-density lipoprotein cholesterol (HDL-C)					✔	
To increase:						
HDL-C	✔	✔		✔	✔	✔
Homozygous familial hyperlipidemia, as an adjunct to other lipid-lowering treatments (eg, low-density lipoprotein (LDL) apheresis) or if such treatments are unavailable	✔				✔ (Adult patients)	✔
To reduce:						
TC	✔				✔	✔
LDL-C	✔				✔	✔
Apo B					✔	
Primary dysbetalipoproteinemia (Fredrickson Type III)	✔	**	**	✔ #	**	✔
Hypertriglyceridemia, elevated serum TG levels (Fredrickson Type IV)	✔	**	**	✔	✔ (Adult patients)	✔
Elevated chylomicrons (Fredrickson Types I and V)	**	**	**		**	**
Heterozygous familial hypercholesterolemia (HeFH) in pediatric patients††	✔ # (10-17 years old) (boys and postmenarchal girls)	✔ # (10-16 years old) (boys and post-menarchal girls)	✔ # (10-17 years old) (boys and post-menarchal girls)	✔ # (>8 years old)		✔ # (10-17 years old) (boys and postmenarchal girls)

TIA=transient ischemic attack
*In adult patients with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease
†In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension
‡In individuals with average to moderately elevated TC and LDL-C, and below average HDL-C
§Hypercholesterolemic patients
ǁ Patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease
¶ The effect of rosuvastatin on cardiovascular morbidity and mortality has not been determined.
#As an adjunct to diet, or after inadequate response to diet and other nonpharmacological measures
**Has not been studied for this condition
††To reduce TC, LDL-C and apolipoprotein B levels if after an adequate trial of diet therapy the following findings are present:
1. LDL-C remains >189 mg/dL or
2. LDL-C remains >160 mg/dL and either (a) there is a positive family history of premature cardiovascular disease (CVD) or (b) 2 or more other CVD risk factors are present

IV. Pharmacokinetics

The pharmacokinetic parameters for the single entity HMG-CoA reductase inhibitors (statins) are summarized in Table 5. Minor clinical differences exist between the statins in regards to pharmacokinetic parameters. All statins possess low systemic bioavailability indicating extensive first-pass metabolism, which is advantageous since the major site of cholesterol synthesis is in the liver. Half-life is one parameter that separates some statins from others. In particular, atorvastatin, fluvastatin sustained-release (SR) and rosuvastatin have long half-lives, allowing for more flexible dose scheduling. All of the statins are available in a dosage form whereby they can be administered once a day.

Table 5. Pharmacokinetic Parameters of the Single Entity HMG-CoA Reductase Inhibitors[2, 4-10,17,18]

Drug(s)	Absolute Bioavailability (%)	Protein Binding (%)	Lipid Solubility	Metabolism	Active Metabolites	Half-Life (hours)
Atorvastatin	14	≥98	Lipophilic	Hepatic, CYP3A4	Yes, 2-hydroxy- and 4-hydroxy-atorvastatin acid	14; metabolites: up to 30
Fluvastatin IR/ fluvastatin SR	IR 24; SR 29	98	Hydrophilic*	Hepatic, CYP2C9 (75%), CYP2C8 (5%), CYP3A4 (20%)	No	IR 2.5-2.8; SR 9
Lovastatin IR/ lovastatin SR	<5; SR/IR=190/100	>95	Lipophilic	Hepatic, CYP3A4	Yes, β-hydroxyacid and 6-hydroxy derivatives	IR 1.1-1.7; SR not reported
Pravastatin	17	50	Hydrophilic	Oxidation, isomerization, conjugation, hydroxylation	No important active metabolites	2.0-3.2; metabolites and parent drug: 77
Rosuvastatin	20	88	Hydrophilic	Hepatic (minor), CYP2C9	Yes, N-desmethyl rosuvastatin	19
Simvastatin	5	95	Lipophilic	Hepatic, CYP3A4	Yes, β-hydroxyacid of simvastatin and its 6′-hydroxy, 6′-hydroxymethyl, and 6′-exomethylene derivatives	Not reported

IR=immediate release, SR=sustained release
*Several sources differed from the package insert, noting fluvastatin to possess lipophilic properties.[19-21]

V. Drug Interactions

Clinically important drug interactions exist for the HMG-CoA reductase inhibitors (statins), with minor differences between the drugs within the class when evaluating their use in the general population. Since atorvastatin, lovastatin and simvastatin are metabolized via CYP3A4, they share similar drug interactions. Fluvastatin and rosuvastatin are primarily metabolized via CYP2C9 whereas pravastatin is not appreciably metabolized by the CYP system. As a result, pravastatin may exhibit a lower potential for drug interactions given its unique metabolism. Significant drug interactions with the single entity statins are listed in Table 6.

Table 6. Significant Drug-Drug Interactions with the Single Entity HMG-CoA Reductase Inhibitors[2,18]

Drug(s)	Significance Level	Interaction	Mechanism
HMG-CoA reductase	1	Amiodarone	Amiodarone may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism via CYP3A4

Drug(s)	Significance Level	Interaction	Mechanism
inhibitors (atorvastatin, lovastatin, simvastatin)			resulting in increased concentration and consequently increased pharmacologic and toxic effects (ie, myositis, rhabdomyolysis) of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin, pravastatin, and rosuvastatin are not significantly metabolized by CYP3A4 and may be safer alternatives.
HMG-CoA reductase inhibitors (all)	1	Azole antifungals (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	Azole antifungal agents may decrease the elimination of HMG-CoA reductase inhibitors by inhibiting their first-pass hepatic metabolism via CYP3A4/CYP2C9 isoenzymes resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of HMG-CoA reductase inhibitors. Itraconazole is contraindicated with HMG-CoA reductase inhibitors metabolized by CYP3A4. If other azole antifungals are to be used, the HMG-CoA reductase inhibitor dose should be decreased accordingly. Patients should be monitored for toxicity. Pravastatin may be a safer alternative since its levels are affected least by azole coadministration.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin)	1	Cyclosporine	Cyclosporine may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism and resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity.
HMG-CoA reductase inhibitors (all)	1	Fibric acid derivatives (fenofibrate, gemfibrozil)	Coadministration of fibric acid derivatives with HMG-CoA reductase inhibitors may result in myopathy or rhabdomyolysis via an unknown mechanism. Decrease HMG-CoA reductase inhibitor dose accordingly; obtain creatine kinase levels and monitor for toxicity.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Grapefruit	Grapefruit may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their first-pass metabolism via CYP3A4, resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of these HMG-CoA reductase inhibitors. Avoid concomitant administration of atorvastatin, lovastatin, and simvastatin with grapefruit products.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Macrolides and ketolides (clarithromycin, erythromycin and telithromycin)	Macrolides may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, myopathy or rhabdomyolysis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin and pravastatin may be safer alternatives.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Nefazodone	Nefazodone may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their metabolism via CYP3A4 resulting in increased concentrations and increased pharmacologic and toxic (ie, rhabdomyolysis or myositis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin and pravastatin may be safer alternatives.
HMG-CoA reductase inhibitors	1	Non-nucleoside reverse transcriptase	Delavirdine and nevirapine may inhibit the metabolism of HMG-CoA reductase inhibitors via CYP3A4, resulting in increased concentration and consequently increased pharmacologic and toxic (ie,

Drug(s)	Significance Level	Interaction	Mechanism
(atorvastatin, lovastatin, pravastatin, simvastatin)		inhibitors (NNRTIs) (delavirdine, efavirenz, nevirapine)	rhabdomyolysis or myopathy) effects of HMG-CoA reductase inhibitors. In contrast, efavirenz may induce CYP3A4 metabolism, resulting in decreased concentration and consequently decreased pharmacologic effects of HMG-CoA reductase inhibitors. With concurrent administration, adjust HMG-CoA reductase inhibitor dose accordingly; monitor plasma low-density lipoprotein cholesterol level, and adverse effects.
Lovastatin	1	Protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir)	Protease inhibitors may decrease the elimination of lovastatin by inhibiting its metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of lovastatin. Decrease lovastatin dose accordingly; monitor for toxicity. Lovastatin is contraindicated in patients receiving concomitant nelfinavir. In addition, lovastatin should not be coadministered with ritonavir, atazanavir, or darunavir.
Pravastatin	1	Protease inhibitors (nelfinavir, ritonavir, saquinavir)	Protease inhibitors may increase the elimination of pravastatin by inducing its metabolism via glucuronidation resulting in decreased concentration and consequently decreased pharmacologic effects of pravastatin. Monitor patients for a decrease in clinical effect with coadministration of pravastatin and certain protease inhibitors.
Simvastatin	1	Protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir)	Protease inhibitors may decrease the elimination of simvastatin by inhibiting its metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of simvastatin. Simvastatin is contraindicated in patients receiving nelfinavir. In addition, coadministration of simvastatin with ritonavir or darunavir should be avoided.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Carbamazepine	Carbamazepine may increase the clearance of certain HMG-CoA reductase inhibitors by inducing their metabolism via CYP3A4 resulting in decreased concentration and consequently decreased pharmacologic effects of HMG-CoA reductase inhibitors. Monitor patients for a decrease in clinical effect. Pravastatin and rosuvastatin may be safer alternatives.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Diltiazem	Diltiazem may decrease the elimination of certain HMG-CoA reductase inhibitors by inhibiting their first-pass metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis, myositis) effects of HMG-CoA reductase inhibitors. Pravastatin may be a safer alternative.
HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin)	2	Rifamycins (rifabutin, rifampin, rifapentine)	Rifamycins may increase the clearance of certain HMG-CoA reductase inhibitors by inducing their first-pass metabolism via CYP3A4 resulting in decreased concentration and consequently decreased pharmacologic effects of HMG-CoA reductase inhibitors. The dose of the HMG-CoA reductase inhibitor may need to be increased. Pravastatin levels may be increased in some patients.
HMG-CoA	2	Verapamil	Verapamil may decrease the elimination of certain HMG-CoA

Drug(s)	Significance Level	Interaction	Mechanism
reductase inhibitors (atorvastatin, lovastatin, simvastatin)			reductase inhibitors by inhibiting their first-pass metabolism via CYP3A4 resulting in increased concentration and consequently increased pharmacologic and toxic (ie, rhabdomyolysis, myositis) effects of HMG-CoA reductase inhibitors. Decrease HMG-CoA reductase inhibitor dose accordingly; monitor for toxicity. Fluvastatin and pravastatin may be safer alternatives.
HMG-CoA reductase inhibitors (fluvastatin, lovastatin, rosuvastatin, simvastatin)	2	Warfarin	HMG-CoA reductase inhibitors may decrease the elimination of warfarin by inhibiting its hepatic metabolism resulting in increased anticoagulant effect of warfarin. Monitor patients' anticoagulant parameters when starting or discontinuing concurrent therapy with warfarin and HMG-CoA reductase inhibitors. Atorvastatin and pravastatin may be safer alternatives.
Atorvastatin	2	Protease inhibitors (amprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir)	Protease inhibitors may decrease the elimination of atorvastatin by inhibiting its first-pass metabolism via CYP3A4 resulting in increased concentrations and consequently increased pharmacologic and toxic (ie, rhabdomyolysis) effects of atorvastatin. Monitor patients receiving atorvastatin for toxicity, especially with ritonavir/saquinavir combination. Decrease atorvastatin dose accordingly; monitor for toxicity.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

HMG-CoA reductase inhibitors (statins) are generally well tolerated with only mild side effects, such as abdominal pain, constipation, flatulence, and headache.[1,2,4-10,18] Patients who do not tolerate one statin may experience improved tolerability with another. More serious but rare side effects of statins include increases in liver enzymes and myopathy (defined as muscle ache in conjunction with creatine kinase [CK] elevation >10 times the upper limit of normal [ULN]), which can progress to rhabdomyolysis and acute renal failure secondary to myoglobinuria. Age >65 years, poorly controlled hypothyroidism, and renal impairment may increase the risk of myopathy among patients taking statins. In clinical trials with rosuvastatin, doses above the recommended 40 mg maximum daily dose were associated with an increased risk of myopathy and rhabdomyolysis.[9] Increases in hepatic transaminases >3 times the ULN have been reported with each statin (0.5%-2.3%) and also appear to be dose-dependent (risk increases as the statin dose increases).[1] Those abnormalities are reversible with statin discontinuation. Routine liver function monitoring is recommended with each statin. It is suggested that liver function tests be performed before the initiation of therapy, at 12 weeks following change in dose, and semiannually thereafter. Statins are contraindicated in patients with active liver disease, including those with unexplained elevations of hepatic transaminase levels. In June 2004, in response to labeling changes in the European Union for rosuvastatin, the FDA reviewed the need to adjust rosuvastatin package labeling in the United States (US) to highlight the risk of myopathy. The FDA reviewed postmarketing adverse event reports and found the labeling current at that time to be sufficient.[22] However, the FDA advisory reinforced the importance of following the recommendations stated in the product label.

The most common adverse reactions reported with the single entity statins are noted in Table 7.

Table 7. Adverse Drug Events (%) Reported with the Single Entity HMG-CoA Reductase Inhibitors [2,4-10,17]

Adverse Event	Atorva-statin	Fluvastatin/ Fluvastatin SR*	Lovastatin/ Lovastatin SR*	Prava-statin	Rosuva-statin	Simva-statin*
Cardiovascular						
Angina pectoris	<2	-	-	3.1	-	-

Adverse Event	Atorva-statin	Fluvastatin/ Fluvastatin SR*	Lovastatin/ Lovastatin SR*	Prava-statin	Rosuva-statin	Simva-statin*
Arrhythmia	<2	-	-	-	-	-
Chest pain	≥2	-	0.5-1.0/–	0.1-2.6	-	-
Hypertension	<2	-	-	-	-	-
Migraine	<2	-	-	-	-	-
Phlebitis	<2	-	-	-	-	-
Palpitation	<2	-	-	-	-	-
Postural hypotension	<2	-	-	-	-	-
Vasodilatation	<2	-	-	-	-	-
Syncope	<2	-	-	-	-	-
Central Nervous System/Neurological						
Abnormal dreams	<2	-	-	-	-	-
Amnesia	<2	-	-	-	-	-
Anxiety	-	✔	✔	1.0	-	✔
Chills	-	✔	✔	✔	-	✔
Cranial nerve dysfunction	-	✔	✔	✔	-	✔
Depression	<2	✔	✔	1.0	-	✔
Dizziness	≥2	✔	0.5-1.2/2	1.0-2.2	≤4	✔
Emotional lability	<2	-	-	-	-	-
Facial paralysis/paresis	<2	✔	-	✔	-	✔
Fever	<2	✔	✔	<1.0	-	✔
Flushing	-	✔	✔	<1.0	-	✔
Headache	2.5-16.7	8.9/4.7	2.1-3.2/7	1.7-1.9	3.1-8.5	3.5
Hyperkinesia	<2	-	-	-	-	-
Hypertonia	<2	-	-	-	-	-
Hypesthesia	<2	-	-	-	-	-
Impairment of extraocular movement	-	✔	-	✔	-	-
Incoordination	<2	-	-	-	-	-
Insomnia	≥2	2.7/0.8	0.5-1.0/–	1.0	-	✔
Libido decreased	<2	✔	✔	<1.0	-	✔
Memory loss	-	✔	✔	<1.0	✔	✔
Neck rigidity	<2	-	-	-	-	-
Paresthesia	<2	✔	0.5-1.0/–	<1.0	-	✔
Peripheral nerve palsy	-	✔	✔	✔	-	✔
Peripheral neuropathy	<2	✔	✔	<1.0	-	✔
Psychiatric disturbances	-	✔	✔	-	-	✔
Somnolence	<2	-	-	-	-	-
Torticollitis	<2	-	-	-	-	-
Tremor	-	✔	✔	<1.0	-	✔
Vertigo	-	✔	✔	<1.0	-	✔
Dermatological						
Acne	<2	-	-	-	-	-
Alopecia	<2	✔	0.5-1.0/–	<1.0	-	✔
Contact dermatitis	<2	-	-	-	-	-
Dry skin	<2	✔	✔	<1.0	-	✔
Eczema	<2	-	-	-	-	0.8
Erythema multiforme	<2	✔	✔	✔	-	✔
Pruritus	<2	✔	0.5-1.0/–	<1.0	<2	0.5
Rash	1.1-3.9	-	0.8-1.3/–	1.3-2.1	<2	0.6
Seborrhea	<2	-	-	-	-	-

Adverse Event	Atorva-statin	Fluvastatin/ Fluvastatin SR*	Lovastatin/ Lovastatin SR*	Prava-statin	Rosuva-statin	Simva-statin*
Skin ulcer	<2	-	-	-	-	-
Stevens-Johnson syndrome	✔	✔	✔	✔	-	✔
Sweating	<2	-	-	-	-	-
Toxic epidermal necrolysis	✔	✔	✔	✔	-	✔
Urticaria	<2	✔	✔	<1.0	<2	-
Endocrine and Metabolic						
Gout	<2	-	-	-	-	-
Hyperglycemia	<2	-	-	-	-	-
Hypoglycemia	<2	-	-	-	-	-
Peripheral edema	≥2	-	-	-	-	-
Weight gain	<2	-	-	-	-	-
Gastrointestinal						
Abdominal pain	0.0-3.8	4.9/3.7	2.0-2.5/–	2.0-2.4	≤2.4	0.9-3.2
Acid regurgitation	-	-	0.5-1.0/–	-	-	-
Anorexia	<2	✔	✔	-	-	✔
Biliary pain	<2	-	-	-	-	-
Cheilitis	<2	-	-	-	-	-
Cholestatic jaundice	<2	✔	✔	✔	✔	✔
Cirrhosis	-	✔	✔	✔	-	✔
Colitis	<2	-	-	-	-	-
Constipation	0.0-2.5	-	2.0-3.5/–	1.2-2.4	2.1-4.7	2.3
Diarrhea	0.0-5.3	4.9/3.3	2.2-2.6/3	2.0	-	0.5-1.9
Decreased appetite	-	-	-	<1.0	-	-
Dry mouth	<2	-	0.5-1.0/–	-	-	-
Duodenal ulcer	<2	-	-	-	-	-
Dyspepsia/heartburn	1.3-2.8	7.9/3.5	1.0-1.6/–	2.0-3.5	-	0.6-1.1
Dysphagia	<2	-	-	-	-	-
Enteritis	<2	-	-	-	-	-
Eructation	<2	-	-	-	-	-
Esophagitis	<2	-	-	-	-	-
Flatulence	1.1-2.8	2.6/1.4	3.7-4.5	1.2-2.7	-	0.9-1.9
Fulminant hepatic necrosis	-	✔	✔	✔	-	✔
Gastritis	<2	-	-	-	-	-
Gastroenteritis	<2	-	-	-	-	-
Glossitis	<2	-	-	-	-	-
Gum hemorrhage	<2	-	-	-	-	-
Hepatitis	<2	✔	✔	✔	✔	✔
Hepatoma	-	✔	✔	✔	-	✔
Increased appetite	<2	-	-	-	-	-
Melena	<2	-	-	-	-	-
Mouth ulceration	<2	-	-	-	-	-
Nausea	≥2	3.2/2.5	1.9-2.5	-	0.0-6.3	0.4-1.3
Nausea/vomiting	-	-	-	1.6-2.9	-	-
Pancreatitis	<2	✔	✔	✔	<2	✔
Rectal hemorrhage	<2	-	-	-	-	-
Stomach ulcer	<2	-	-	-	-	-
Stomatitis	<2	-	-	-	-	-
Tenesmus	<2	-	-	-	-	-
Ulcerative stomatitis	<2	-	-	-	-	-

Adverse Event	Atorva-statin	Fluvastatin/ Fluvastatin SR*	Lovastatin/ Lovastatin SR*	Prava-statin	Rosuva-statin	Simva-statin*
Vomiting	<2	✔	0.5-1.0/–	-	-	✔
Genitourinary						
Abnormal ejaculation	<2	-	-	-	-	-
Albuminuria	≥2	-	-	-	-	-
Breast enlargement	<2	-	-	-	-	-
Cystitis	<2	-	-	-	-	-
Dysuria	<2	-	-	<1.0	-	-
Epididymitis	<2	-	-	-	-	-
Erectile dysfunction	-	✔	✔	<1.0	-	✔
Fibrocystic breast	<2	-	-	-	-	-
Gynecomastia	-	✔	✔	✔	-	✔
Hematuria	≥2	-	-	-	-	-
Impotence	<2	-	-	-	-	-
Kidney calculus	<2	-	-	-	-	-
Metrorrhagia	<2	-	-	-	-	-
Nephritis	<2	-	-	-	-	-
Nocturia	<2	-	-	<1.0	-	-
Urinary abnormality	-	-	-	0.7-1.0	-	-
Urinary frequency	<2	-	-	<1.0	-	-
Urinary incontinence	<2	-	-	-	-	-
Urinary retention	<2	-	-	-	-	-
Urinary tract infection	≥2	1.6/2.7	–/2	-	-	-
Urinary urgency	<2	-	-	1.0	-	-
Uterine hemorrhage	<2	-	-	-	-	-
Vaginal hemorrhage	<2	-	-	-	-	-
Hematologic						
Anemia	<2	-	-	-	-	-
Ecchymosis	<2	-	-	-	-	-
Eosinophilia	-	✔	✔	✔	-	✔
Hemolytic anemia	-	✔	✔	✔	-	✔
Leukopenia	-	✔	✔	✔	-	✔
Lymphadenopathy	<2	-	-	-	-	-
Petechia	<2	-	-	-	-	-
Purpura	-	✔	✔	✔	-	✔
Thrombocytopenia	<2	✔	✔	-	-	✔
Vasculitis	-	✔	✔	✔	-	✔
Laboratory Test Abnormalities						
Bilirubin elevation	-	✔	✔	-	✔	✔
Creatine phosphokinase increased	<2	-	-	-	2.6	✔
Eosinophil sedimentation rate increase	-	✔	✔	✔	-	✔
Hematuria	-	-	-	-	✔	-
Liver enzyme abnormalities	-	✔	✔	✔	2.2	✔
Positive antinuclear antibody	-	✔	✔	✔	-	✔
Proteinuria	-	-	-	-	✔	-
Thyroid level abnormality	-	✔	✔	✔	✔	✔
Musculoskeletal						
Arthralgia	0.0-5.1	–/3.2	0.5-1.0/5	6.0	10.1	✔
Arthritis	≥2	2.1/1.3	0.5-6/5.0	✔	-	✔
Back pain	0.0-3.8	-	–/5	-	-	-

Adverse Event	Atorva-statin	Fluvastatin/ Fluvastatin SR*	Lovastatin/ Lovastatin SR*	Prava-statin	Rosuva-statin	Simva-statin*
Bursitis	<2	-	-	-	-	-
Dermatomyositis	-	-	-	✔	-	-
Leg cramps	<2	-	-	-	-	-
Leg pain	-	-	0.5-1.0/–	-	-	-
Localized pain	-	-	-	1.4	-	-
Muscle cramps	-	✔	0.6-1.1/–	2.0	-	✔
Myalgia	0.0-5.6	5.0/3.8	1.8-3.0/3	0.6-1.4	1.9-12.7	1.2
Myopathy	-	✔	-	✔	-	✔
Myositis	<2	-	-	-	-	-
Myasthenia	<2	-	-	<1.0	-	-
Polymyalgia rheumatica	-	✔	✔	✔	-	✔
Rhabdomyolysis	✔	✔	✔	✔	-	✔
Shoulder pain	-	-	0.5-1.0/–	-	-	-
Tendinous contracture	<2	-	-	-	-	-
Tenesynovitis	<2	-	-	-	-	-
Respiratory						
Asthma	<2	-	-	-	-	-
Bronchitis	≥2	1.8/2.6	-	-	-	-
Cough	-	-	-	0.1-1.0	-	-
Dyspnea	<2	✔	✔	1.6	-	✔
Epistaxis	<2	-	-	-	-	-
Pharyngitis	0.0-2.5	-	-	-	-	-
Pneumonia	<2	-	-	-	-	-
Rhinitis	≥2	-	-	0.1	-	-
Sinusitis	0.0-6.4	2.6/3.5	-/4	-	-	-
Upper respiratory infection	-	-	-	1.3	-	2.1
Other						
Accidental injury	0.0-4.2	5.1/4.2	-/6	-	-	-
Allergic reaction	0.0-2.8	2.3/1.0	-	<1.0	-	-
Amblyopia	<2	-	-	-	-	-
Anaphylaxis	✔	✔	✔	✔	-	✔
Angioedema	-	✔	✔	✔	<2	✔
Angioneurotic edema	✔	-	-	-	-	-
Asthenia	0.0-3.8	✔	1.2-2.0/3	✔	0.9-4.7	1.6
Blurred vision	-	-	0.9-1.2/–	-	-	-
Cataracts	-	✔	✔	-	-	0.5
Deafness	<2	-	-	-	-	-
Dry eyes	<2	-	-	-	-	-
Eye hemorrhage	<2	-	-	-	-	-
Eye irritation	-	-	0.5-1.0/–	-	-	-
Facial/general edema	<2	-	-	<1.0	-	-
Fatigue	✔	2.7/1.6	-	1.9-3.4	-	-
Flu syndrome	0.0-3.2	5.1/7.1	-/5	-	-	-
Glaucoma	<2	-	-	-	-	-
Infection	2.8-10.3	-	-/11	-	-	-
Lens opacity	-	-	-	<1.0	-	-
Lupus erythematosus-like syndrome	-	✔	✔	✔	-	✔
Malaise	<2	✔	✔	✔	-	✔
Ophthalmoplegia	-	✔	✔	-	-	✔

Adverse Event	Atorva-statin	Fluvastatin/ Fluvastatin SR*	Lovastatin/ Lovastatin SR*	Prava-statin	Rosuva-statin	Simva-statin*
Pain	-	-	-/3	-	-	-
Parosmia	<2	-	-	-	-	-
Photosensitivity reaction	<2	✔	✔	✔	-	-
Refraction disorder	<2	-	-	-	-	-
Taste loss	<2	-	-	-	-	-
Taste disturbance	<2	✔	-	<1.0	-	-
Tinnitus	<2	-	-	-	-	-
Visual disturbance	-	-	✔	1.6	-	-
Weight loss	-	-	-	-	-	-

*Checks in this column refer to adverse events reported with drugs in this class, but not to the specific agent.
✔ Percent not specified
-Event not reported or incidence <1%

VII. Dosing and Administration

The usual dosing regimens for the single entity HMG-CoA reductase inhibitors (statins) are summarized in Table 8. All statins are dosed once daily with the exception of maximum doses of lovastatin and fluvastatin immediate-release products, which should be divided into twice-daily dosing. Atorvastatin, rosuvastatin, and fluvastatin sustained-release are the only statins that may be administered at any time in the day. The other statins should be administered in the evening or at bedtime to target the time of maximum cholesterol synthesis.

Table 8. Usual Dosing for the Single Entity HMG-CoA Reductase Inhibitors[2,4-10,17]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Atorvastatin	Hypercholesterolemia; heterozygous familial/nonfamilial hypercholesterolemia; secondary prevention of cardiovascular events: Initial, 10-20 mg once daily; maximum, 80 mg daily. For low-density lipoprotein cholesterol (LDL-C) reduction >45%, initiate at 40 mg once daily. Primary prevention of cardiovascular events: Initial, 10 mg once daily Homozygous familial hypercholesterolemia: 10-80 mg once daily Hypertriglyceridemia: Initial, 10 mg once daily; maximum, 80 mg daily	Heterozygous familial hypercholesterolemia: (Adolescents 10-17 years old): Initial, 10 mg once daily; maximum, 20 mg daily Homozygous familial hypercholesterolemia: Initial, 10 mg once daily; maximum, 80 mg daily Safety and efficacy in children younger than 10 years of age have not been established.	Tablet: 10 mg 20 mg 40 mg 80 mg
Fluvastatin/ fluvastatin SR	Coronary arteriosclerosis: Capsule: initial, 40 mg once or twice daily (LDL-C reduction goal of ≥25%) or 20 mg once daily in the evening (LDL-C reduction goal of <25%); maintenance, 20-80 mg daily, divided into 2 daily doses Sustained-release tablet: 80 mg once daily Primary hypercholesterolemia, heterozygous familial and nonfamilial and mixed lipidemia and LDL-C reduction goal of ≥25%: Capsule: initial, 40 mg once or twice daily; maintenance, 20-80 mg daily	Heterozygous familial hypercholesterolemia: (Adolescents 10-16 years old): Initial: 20 mg capsule once daily in the evening; maintenance, 20-80 mg daily; maximum, 80 mg daily, either two 40 mg capsules in divided doses, or one sustained-release tablet Safety and efficacy in children younger than 10 years of age have not been established.	Capsule: 20 mg 40 mg Sustained-release tablet: 80 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Sustained-release tablet: initial, 80 mg once daily Patients with LDL-C reduction goal of ≤25%: Capsule: as above, except that a starting dose of 20 mg/day may be used		
Lovastatin/ lovastatin SR	Hypercholesterolemia, primary and mixed: Tablet: initial, 20 mg once daily at bedtime; maximum, 80 mg daily, in two divided doses Sustained-release tablet: 20-60 mg once daily at bedtime Coronary arteriosclerosis: Tablet: initial, 20 mg once daily at bedtime; maximum, 80 mg daily, in two divided doses Sustained-release tablet: 20-60 mg once daily at bedtime Coronary arteriosclerosis, primary; prophylaxis: Tablet: initial, 20 mg once daily at bedtime; maintenance, 10-80 mg; maximum, 80 mg daily, in two divided doses Sustained-release tablet: 20-60 mg once at bedtime	Heterozygous familial hypercholesterolemia: (Adolescents 10-17 years old): Tablet: initial, 10 mg daily at bedtime; maximum, 40 mg daily Safety and efficacy of doses higher than 40 mg daily have not been established in children. Safety and efficacy of sustained-release tablets have not been established in children.	Sustained-release tablet: 20 mg 40 mg 60 mg Tablet: 10 mg 20 mg 40 mg
Pravastatin	Hyperlipidemia: Initial, 40 mg once daily at bedtime; maintenance, 40-80 mg once daily Primary prevention of cardiovascular events: 40 mg once daily at bedtime Secondary prevention of cardiovascular events: 40 mg once daily at bedtime	Heterozygous familial hypercholesterolemia: (8-13 years old): 20 mg once daily at bedtime Doses greater than 20 mg daily have not been studied in children 8-13 years old. (14-18 years old): 40 mg once daily at bedtime Doses greater than 40 mg daily have not been studied in children 8-13 years old.	Tablet: 10 mg 20 mg 40 mg 80 mg
Rosuvastatin*	Hyperlipidemia, mixed dyslipidemia, hypertriglyceridemia, slowing of the progression of atherosclerosis: Initial, 5-10 mg once daily or 20 mg once daily for patients with LDL-C greater than 190 mg/dL and when aggressive lipid reduction is desired; maintenance, 5-40 mg once daily (the 40 mg dose should be reserved for patients who failed therapy with the 20 mg dose); maximum, 40 mg daily Homozygous familial hypercholesterolemia: Initial, 20 mg once daily; maintenance, 20-40 mg once daily; maximum, 40 mg daily	Safety and efficacy in children younger than 18 years of age have not been established.	Tablet: 5 mg 10 mg 20 mg 40 mg
Simvastatin	Coronary arteriosclerosis; prophylaxis:	Heterozygous familial	Tablet:

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Initial, 20-40 mg once daily in the evening; dose range, 5-80 mg daily Homozygous familial hypercholesterolemia: Initial, 40 mg once daily in the evening or 80 mg daily in 3 divided doses (20 mg, 20 mg, and 40 mg in the evening) Hypercholesterolemia: Initial, 20-40 mg once daily in the evening; dose range, 5-80 mg daily	hypercholesterolemia: (Adolescents 10-17 years old): Initial, 10 mg daily in the evening; maintenance, 10-40 mg daily; maximum, 40 mg daily Safety and efficacy in children younger than 10 years of age or in premenarchal girls have not been established.	5 mg 10 mg 20 mg 40 mg 80 mg

*Lower initial dose should be considered for patients requiring less aggressive LDL-C reduction, predisposed to myopathy, taking cyclosporine, gemfibrozil, or lopinavir/ritonavir, Asian patients, and patients with severe renal insufficiency.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the single entity HMG-CoA reductase inhibitors (statins) are summarized in Table 9.

Table 9. Comparative Clinical Trials Using the Single Entity HMG-CoA Reductase Inhibitors

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Delaying the Progression of Atherosclerosis				
Furberg et al[23] ACAPS Lovastatin 20 to 40 mg once daily in addition to warfarin 1 mg once daily vs lovastatin 20 to 40 mg once daily in addition to warfarin placebo once daily vs lovastatin placebo once daily in addition to warfarin 1 mg once daily vs lovastatin placebo once daily in addition to warfarin placebo once daily	DB, MC, PC, RCT Asymptomatic men and women 40 to 79 years old, with early carotid atherosclerosis as defined by B-mode ultrasonography and moderately elevated LDL cholesterol (LDL levels between the 60th and 90th percentiles)	N=919 3 years	Primary 3-year change in the mean maximum IMT in 12 walls of the carotid arteries (near and far walls of the common carotid, the bifurcation, and the internal carotid arteries on both sides of the neck) Secondary Change in single maximum IMT, incidence of major cardiovascular events and adverse events	Primary The progression rate of mean maximum IMT was less in the lovastatin and warfarin combination group than in the lovastatin group alone (*P*=0.04). The overall annualized progression rates of mean maximum IMT in the lovastatin group and placebo group were –0.009 and 0.006 mm/year, respectively (*P*=0.001). Secondary: The changes in single maximum IMT in the lovastatin group and placebo group were –0.036±0.022 mm/year and 0.000±0.011 mm/year, respectively (*P*=0.12). Fourteen of the 459 patients in the lovastatin-placebo groups had a major cardiovascular event (4 CHD deaths, 5 strokes and 5 nonfatal myocardial infarction) compared with 5 of the 460 patients in the lovastatin group (*P*=0.04). There was 1 death in patients treated with lovastatin and 8 deaths in patients receiving lovastatin-placebo therapy (*P*=0.02). All 6 cardiovascular deaths were in the lovastatin-placebo group, the remaining 3 deaths were cancer deaths. The lovastatin and lovastatin-placebo groups showed no difference in ALT elevations of ≥200% the ULN.
Byington et al[24] PLAC-II	DB, PC, RCT Patients with a history of CHD and ≥1	N=151 3 years	Primary: Change in the mean of maximum IMT measurements in the	Primary: Pravastatin treatment did not result in a statistically significant reduction in the progression of mean maximum IMT (*P*=0.44).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Pravastatin 20 mg once daily in the evening, titrated up to 40 mg daily vs placebo once daily in the evening	extracranial carotid lesion with the maximum IMT ≥1.3 mm		common, internal, and bifurcation carotid artery segments Secondary: Effects on individual carotid artery segments and clinical events	Pravastatin treatment was associated with a 35% statistically significant reduction in IMT progression in the common carotid artery (*P*=0.03). There was no significant effect on bifurcation (*P*=0.49) or on the internal carotid artery (*P*=0.93) with pravastatin therapy. Secondary: Pravastatin treatment was associated with a 60% reduction in clinical coronary events (*P*=0.09). When compared to placebo, a significant 61% reduction in the incidence of any coronary events and all-cause mortality was seen in the pravastatin group (*P*=0.04).
Crouse et al[25] METEOR Rosuvastatin 40 mg once daily vs placebo once daily	DB, RCT Adult patients between the ages of 45 and 70 years, with LDL-C between 120 and 190 mg/dL among patients whose only CHD risk factor was age, and an LDL-C between 120 and 160 mg/dL for individuals with ≥2 CHD risk factors and a 10-year risk of CHD events of <10%, HDL-C level ≤60 mg/dL, level of TG <500 mg/dL, and maximum CIMT between 1.2 mm and 3.5 mm from 2 separate ultrasounds;	N=984 2 years	Primary: Annualized rate of change in maximum CIMT of the 12 carotid artery sites (near and far walls of the right and left common carotid artery, carotid bulb, and internal carotid artery) Secondary: Annualized rate of change in maximum CIMT of the common carotid artery, carotid bulb, and internal carotid artery sites, and annualized rate of change in mean	Primary: Rosuvastatin therapy was associated with a significant reduction in the annualized rate of change in maximum CIMT from baseline compared with placebo (*P*<0.001). Secondary: Rosuvastatin therapy was associated with a statistically significant 49% reduction in LDL-C from baseline compared with placebo (*P*<0.001). Rosuvastatin therapy was associated with a statistically significant reduction in the annualized rate of change in the maximum CIMT for the common carotid artery sites (*P*<0.001), carotid bulb (*P*<0.001), and internal carotid artery sites (*P*=0.02) from baseline compared with placebo. Rosuvastatin therapy was associated with a statistically significant reduction in the annualized rate of change in the mean CIMT for the common carotid artery sites (*P*<0.001) from baseline compared with placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	patients were excluded if they had used lipid-lowering therapies in the previous 12 months, had clinical evidence of CAD or other peripheral atherosclerotic disease, prior revascularization procedures, 10-year CHD risk ≥10%, diabetes, uncontrolled hypertension or familial hypercholesterolemia, or serum creatinine >2 mg/dL		CIMT	
Nissen, Nicholls et al[26] ASTEROID Rosuvastatin 40 mg once daily	MC, OL, PRO Patients ≥18 years old, requiring coronary angiography for a stable or unstable ischemic chest pain syndrome or abnormal exercise test, with ≥1 obstruction ≥20% angiographic luminal diameter narrowing in a coronary vessel, not on statin therapy for >3 months within the last 12 months; patients were excluded if they had a triglyceride level ≥500 mg/dL or poorly	N=507 24 months	Primary: Percent atheroma volume (PAV), absolute change in total atheroma volume (TAV) in the 10 mm subsegment of the coronary artery with the largest plaque volume at baseline Secondary: Change in normalized TAV, lipid parameters	Primary: With rosuvastatin treatment, patients experienced a significant reduction in PAV from baseline (–0.79%; 95% CI, –1.21% to –0.53%; *P*<0.001). With rosuvastatin treatment, patients experienced a significant reduction from baseline in atheroma volume in the most diseased 10 mm subsegment (–5.6 mm^3; 95% CI, –6.82 mm^3 to –3.96 mm^3; *P*<0.001). Secondary: With rosuvastatin treatment, patients experienced a significant reduction from baseline in normalized TAV (–12.5 mm^3; 95% CI, –15.08 mm^3 to –10.48 mm^3; *P*<0.001). With rosuvastatin treatment, patients experienced a significant reduction from baseline in the total normalized TAV (–6.8%; 95% CI, –7.82% to –5.60%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	controlled diabetes			With rosuvastatin treatment, patients experienced a significant reduction from baseline in TC (33%), LDL-C (53.2%), TG (14.5%), LDL-C:HDL-C ratio (58.5%), and non–HDL-C (47.2%; *P*<0.001). With rosuvastatin treatment, patients experienced a significant increase from baseline in HDL-C (14.7%; *P*<0.001).
Kastelein et al[27] ENHANCE Simvastatin 80 mg daily and placebo vs simvastatin 80 mg daily and ezetimibe 10 mg daily	DB, MC, PRO, RCT Men and women between the ages of 30 and 75 years with FH regardless of their previous treatment with lipid-lowering drugs, baseline LDL-C at least 210 mg/dL without treatment; patients were excluded if they had high-grade stenosis or occlusion of the carotid artery, history of carotid endarterectomy or carotid stenting, homozygous FH, NYHA class III or IV congestive heart failure, cardiac arrhythmia, angina pectoris or recent cardiovascular events	N=720 24 months (plus 6-week run-in period with placebo)	Primary Change in mean carotid artery IMT (defined as average of means of far wall IMT of right and left common carotid arteries and bulbs and internal carotid arteries) Secondary: Proportion of patients with regression in the mean carotid artery IMT or new carotid artery plaques of more than 1.3 mm, change from baseline in mean maximal carotid artery IMT and average mean IMT of carotid and common femoral arteries, lipid parameters, CRP, adverse events	Primary The mean change in the carotid artery IMT was 0.0058±0.0037 mm in the simvastatin monotherapy group and 0.0111±0.0038 mm in the simvastatin-ezetimibe group (*P*=0.29). Secondary: There was no significant difference in the proportion of patients with regression in the mean carotid artery IMT (44.4% vs 45.3%; *P*=0.92) or new plaque formation (2.8% vs 4.7%; *P*=0.20) receiving simvastatin vs simvastatin-ezetimibe, respectively. No significant change from baseline was reported in the mean maximum carotid artery IMT (0.0103±0.0049 mm and 0.0175±0.0049 mm, respectively; *P*=0.27). No significant changes were observed between study groups regarding mean measures of IMT of the common carotid artery (*P*=0.93), carotid bulb (*P*=0.37), internal carotid artery (*P*=0.21) and femoral artery (*P*=0.16) or average of the mean values for carotid and femoral artery IMT (*P*=0.15). After 24 months, mean LDL-C decreased by 39.1 mg/dL in the simvastatin group and by 55.6 mg/dL in the combination group (between-group difference of 16.5%; *P*<0.01). Reductions in TG (between-group difference of 6.6%; *P*<0.01) and CRP (between-group difference of 25.7%; *P*<0.01) were significantly higher with simvastatin-ezetimibe than simvastatin alone.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Adverse events (29.5% vs 34.2%; *P*=0.18) and discontinuation rates (9.4% vs 8.1%; *P*=0.56) were similar between simvastatin monotherapy and the combination therapy.
Yu et al[28] Atorvastatin 80 mg once daily vs atorvastatin 10 mg once daily	DB, RCT Patients with CHD (confirmed by angiographic evidence of coronary stenosis, previous MI, PCI, or angina pectoris), hypercholesterolemia and an LDL-C >100 mg/dL	N=112 26 weeks	Primary: Improvement in IMT Secondary: Reduction in CRP level, and proinflammatory cytokines at week 26	Primary: While atorvastatin 10 mg therapy was not associated with a statistically significant improvement in either left or right carotid IMT (*P* value not reported), atorvastatin 80 mg therapy led to a significant improvement in left carotid IMT (*P*=0.02) as well as the right carotid IMT from baseline (*P*=0.01). Secondary: While atorvastatin 10 mg therapy was not associated with a statistically significant change in CRP (*P* value not reported), atorvastatin 80 mg therapy led to a significant reduction in CRP level from baseline (*P*=0.01). In terms of proinflammatory cytokines, atorvastatin 10 mg therapy was associated with a statistically significant reduction in interleukin-8 (*P*=0.01), interleukin-18 (*P*<0.001), and tumor necrosis factor (*P*<0.001). Atorvastatin 80 mg therapy led to a significant reduction in all the proinflammatory cytokines from baseline (*P*<0.05).
Schmermund et al[29] Atorvastatin 10 mg once daily vs atorvastatin 80 mg once daily	DB, MC, RCT Patients between the ages of 32 and 80 years without a history of MI, coronary revascularization, or hemodynamically relevant stenoses, with moderate calcified coronary atherosclerosis (coronary artery calcification [CAC]	N=471 12 months	Primary: The percent change in total CAC volume score Secondary: Change in LDL-C	Primary: There was no significant difference in the primary end point between the two groups (*P*=0.6477). Secondary: Atorvastatin 80 mg therapy was associated with a 20% reduction in LDL-C compared to atorvastatin 10 mg therapy (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	score ≥30), LDL-C between 130 and 250 mg/dL in the absence of statin therapy or between 100 and 130 mg/dL under statin therapy, TG <400 mg/dL, ≥2 cardiovascular risk factors			
Nissen, Tuzcu, Schoenhagen, Brown et al[30] REVERSAL Atorvastatin 40 mg twice daily vs pravastatin 40 mg once daily in addition to placebo once daily	DB, MC, RCT Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C between 125 and 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long	N=654 18 months	Primary: Percentage change in atheroma volume from baseline Secondary: Nominal change in atheroma volume, nominal change in atheroma volume in the 10 contiguous cross-sections with the greatest and the least atheroma volume	Primary: Atorvastatin therapy was associated with a significant delay in atheroma volume progression compared to pravastatin therapy (*P*=0.02). Secondary: Atorvastatin therapy was associated with a significant nominal change in total atheroma volume compared to pravastatin therapy (*P*=0.02). Atorvastatin therapy was associated with a significant change in the percentage of atheroma volume compared to pravastatin therapy (*P*<0.001). Atorvastatin therapy was associated with a significant change in atheroma volume in the most severely diseased 10 mm vessel subsegment compared to pravastatin therapy (*P*=0.01). Progression of coronary atherosclerosis from baseline occurred in the 2.7% of the pravastatin-treated patients (*P*=0.001) and none of the atorvastatin-treated patients (*P*=0.98). Atorvastatin 80 mg daily therapy was associated with a significant reduction in TC, LDL-C, TG, apo B, and CRP (*P*<0.001) compared with the pravastatin group.
Schoenhagen et al[31]	DB, MC, RCT	N=654	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
REVERSAL Atorvastatin 40 mg twice daily vs pravastatin 40 mg once daily in addition to placebo once daily	Serial intravascular ultrasound observations from the REVERSAL study. Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C between 125 and 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long	18 months	Percentage change from baseline in external elastic membrane area lesion, lumen area lesion, plaque area lesion, remodeling ratio Secondary: Not reported	Atorvastatin therapy was associated with a significant 6.6% increase in the external elastic membrane area lesion from baseline (*P*<0.0001). Atorvastatin therapy was associated with a significant 7.3% increase in the lumen area lesion from baseline (*P*=0.0002). Atorvastatin therapy was associated with a significant 7.9% increase in the plaque area lesion from baseline (*P*=0.0002). Atorvastatin therapy was associated with a significant 3.3% reduction in remodeling ratio from baseline (*P*=0.024). Pravastatin therapy was associated with a significant 9% increase in the external elastic membrane area lesion from baseline (*P*=0.0002). Pravastatin therapy was associated with a significant 9.5% increase in the lumen area lesion from baseline (*P*=0.0003). Pravastatin therapy was associated with a significant 9.9% increase in the plaque area lesion from baseline (*P*=0.0022). Pravastatin therapy was associated with a significant 2.7% reduction in remodeling ratio from baseline (*P*=0.0013). There was no statistically significant difference between the atorvastatin intensive therapy and the pravastatin groups in terms of increase in plaque area from baseline (7.9% vs 9.9%, respectively; *P*=0.57). There was no statistically significant difference between the atorvastatin (intensive) therapy and the pravastatin (moderate) groups in terms of reduction in remodeling ratio from baseline (3.3% vs 2.7%, respectively; *P*=0.68). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Nicholls et al[32] REVERSAL Atorvastatin 40 mg twice daily vs pravastatin 40 mg once daily in addition to placebo once daily	DB, MC, RCT, SA Subanalysis of REVERSAL study in obese patients. Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C between 125 and 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long, stratified based on BMI>29.6 kg/m^2 or BMI<29.6 kg/m^2	N=654 18 months	Primary: Percentage change from baseline in lipid parameters, atheroma volume Secondary: Not reported	Primary: Compared to the BMI<29.6 kg/m^2 group, obese patients on atorvastatin therapy exhibited a significantly lower reduction in TC (40% vs 36%; *P*=0.007), LDL-C (55% vs 49%; *P*=0.008), and TG (35% vs 23%; *P*=0.04). Compared to the BMI<29.6 kg/m^2 group, obese patients on atorvastatin therapy exhibited a significantly higher reduction in CRP (33% vs 40%; *P*=0.04). There was no significant difference in lipid parameters between the BMI groups among patients randomized to pravastatin therapy (*P*>0.05). Compared to the BMI<29.6 kg/m^2 group, obese patients on atorvastatin therapy exhibited a significantly greater benefit on the total atheroma volume (*P*=0.01) and percent atheroma volume (*P*=0.0005). In contrast, pravastatin therapy was associated with a significant 6.5% increase in atheroma volume in the obese group (*P*=0.006). Secondary: Not reported
Nissen, Tuzcu, Schoenhagen, Crowe et al[33] REVERSAL Atorvastatin 40 mg twice daily vs pravastatin 40 mg once daily in addition to placebo	DB, MC, RCT Subanalysis of REVERSAL study evaluating the effect of statin therapy on LDL, CRP, and CAD. Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major	N=654 18 months	Primary: Percent change in TC, TG, CRP, non–HDL-C, HDL-C, atheroma volume Secondary: Not reported	Primary: Patients in both treatment groups experienced a significant reduction from baseline in the TC (63%; *P*<0.001), LDL-C (56%; *P*<0.001), TG (40%; *P*=0.002), CRP (22.4%; *P*<0.001) and non–HDL-C (33%; *P*<0.001). HDL-C was not significantly increased from baseline in either group (4.2%; *P*=0.11). Patients randomized to atorvastatin experienced a slower rate of disease progression (atheroma volume) compared to patients receiving pravastatin therapy (0.2% vs 1.6%; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
once daily	epicardial coronary artery and an LDL-C between 125 and 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long, stratified based on BMI>29.6 kg/m^2 or BMI<29.6 kg/m^2			Patients whose LDL-C and CRP reductions were greater than the median experienced a significantly slower rate of disease progression compared with patients with lower LDL-C and CRP reductions (*P*=0.001). Secondary: Not reported
Familial Hypercholesterolemia (FH)				
Rodenburg et al[34] Pravastatin 20 mg (children <14 years of age) or pravastatin 40 mg (children ≥14 years of age)	FU Children diagnosed with FH, between 8 and 18 years of age, on a fat-restricted diet ≥3 months, with LDL-C ≥4.0 mmol/L and triglyceride levels <4.0 mmol/L on 2 different occasions, using adequate contraception, not on any treatment for hypercholesterolemia, including plant sterol or stanol products	N=214 2 years (mean duration of total treatment with a statin was 4.5 years)	Primary: Percentage change in TC, LDL-C, TG, HDL-C, predictors of smaller carotid IMT, and safety Secondary: Not reported	Primary: Statin therapy was associated with a 22.5% reduction in TC from baseline (*P* value not reported). Statin therapy was associated with a 29.2% reduction in LDL-C from baseline (*P* value not reported). Statin therapy was associated with a 3.1% increase in HDL-C from baseline (*P* value not reported). Statin therapy was associated with a 1.9% reduction in TG from baseline (*P* value not reported). The study found several independent predictors of smaller carotid IMT: IMT at statin initiation (*P*<0.001), age at statin initiation (*P*=0.016), male sex (*P*<0.001), and the duration of statin therapy (*P*<0.001). Secondary: Not reported
Avis et al[35] Standard statin therapy	MA Randomized, placebo-	N=798 (6 studies)	Primary: Percentage change in TC, LDL-C, TG,	Primary: Statin therapy was associated with a 23% reduction in TC compared with placebo (95% CI, 19 to 27; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(pravastatin, fluvastatin, lovastatin, rosuvastatin, simvastatin, atorvastatin) vs placebo	controlled trials, evaluating statin therapy in patients, aged <18 years, with heterozygous FH; studies were excluded if lipid lowering co-medication was used, if treatment was unblinded, abstracts, or if none of the following outcome measures were reported: lipid profile, IMT, or safety parameters	Up to 2 years	HDL-C, apo B, apo AI, the difference in absolute changes in IMT, and safety Secondary: Not reported	Statin therapy was associated with a 30% reduction in LDL-C compared with placebo (95% CI, 24 to 36; *P* value not reported). Statin therapy was associated with a 3.6% increase in HDL-C compared with placebo (95% CI, 1.33 to 5.94; *P* value not reported). Statin therapy was associated with a 25% reduction in apo B compared with placebo (95% CI, 19 to 31; *P* value not reported). Statin therapy was associated with a 2.4% reduction in apo AI compared with placebo (95% CI, 0.41 to 4.45; *P* value not reported). Statin therapy was associated with a significant carotid IMT regression compared with placebo (*P*=0.02). Statin therapy was not associated with a significant risk of adverse events compared with placebo (RR, 0.99; 95% CI, 0.79 to 1.25; *P* value not reported). Statin therapy was not associated with a significant risk of AST (RR, 0.98; 95% CI, 0.23 to 4.26; *P* value not reported), ALT (RR, 2.03; 95% CI, 0.24 to 16.95; *P* value not reported), or CK elevation (RR, 1.38; 95% CI, 0.18 to 10.82; *P* value not reported) compared with placebo. Secondary: Not reported
Shafiq et al[36] Statins (lovastatin up to 40 mg/day, pravastatin up to 20 mg/day, simvastatin [no dose reported], atorvastatin up to 20 mg/day)	MA Randomized, double-blind, controlled trials comparing statins with placebo in pediatric and adolescent patients with FH	6 studies N=798 12-104 weeks	Primary Percent change in LDL-C, TC, TG, HDL-C Secondary Not reported	Primary Statin therapy was associated with a significant reduction in LDL-C compared with placebo (*P* value not reported). Statin therapy was associated with a significant reduction in TC compared with placebo (*P* value not reported). Statin therapy was associated with a significant reduction in TG

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				compared with placebo (*P* value not reported). Statin therapy was associated with a significant increase in HDL-C compared with placebo (*P* value not reported). Secondary: Not reported
Marais et al[37] Rosuvastatin 80 mg once daily for 6 weeks, following an 18-week open label titration phase during which patients received rosuvastatin 20 mg once daily for 6 weeks, titrated up to 40 mg/day for 6 weeks, titrated up to 80 mg/day for another 6 weeks, after a 4-week dietary lead-in period vs atorvastatin 80 mg once daily for 6 weeks, following an 18-week open label titration phase during which patients received rosuvastatin 20 mg once daily for 6 weeks, titrated up to 40 mg/day for 6 weeks, titrated up to 80 mg/day for another 6 weeks, after a 4-week	RCT, DB, XO Patients >10 years of age, weighing ≥32 kg, with homozygous FH, fasting LDL-C >500 mg/dL, TG <600 mg/dL, and either xanthomata before 10 years of age or both parents with FH; patients were excluded if had active liver disease, unexplained elevations in ALT/AST, bilirubin ≥3 times ULN, unexplained CK >3 times ULN, serum creatinine >220 µmol/L, or uncontrolled hypertension	N=44 24 weeks (16-weeks OL titration phase)	Primary Percent change in LDL-C from baseline to week 18 Secondary Response rate, percent change in TC, apo B, TG, HDL-C	Primary Patients receiving rosuvastatin 20-80 mg experienced a significant reduction in LDL-C from baseline after 18 weeks of therapy (21.4%; *P*<0.0001). Patients without a portacaval shunt and those not receiving plasmaphoresis who were treated with rosuvastatin 20-80 mg experienced a 15% reduction in LDL-C from baseline after 18 weeks of therapy (*P* value not reported). Secondary: Rosuvastatin treatment was associated with an overall 72% response rate, defined as ≥15% reduction in baseline LDL-C (*P* value not reported). Patients receiving rosuvastatin 20-80 mg experienced a significant reduction in TC and apo B from baseline after 18 weeks of therapy (20%; *P*<0.0001). Patients receiving rosuvastatin 20-80 mg experienced a non-significant increase in TG and HDL-C from baseline after 18 weeks of therapy (3.3% and 3.1%, respectively; *P*>0.05). At week 24, patients randomized to rosuvastatin and atorvastatin did not differ in the magnitude of LDL-C reduction from baseline (19.1% vs 18%; *P*=0.67). At week 24, there was no statistically significant difference between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dietary lead-in period				patients randomized to rosuvastatin and atorvastatin in reductions from baseline in TC (17.6% vs 17.9%; *P*=0.91), TG (6.3% vs 13.9%; *P*=0.21), or apo B (11.4% vs 11.7%; *P*=0.90). The only statistically significant difference between the two groups was in apo AI change from baseline. While patients receiving rosuvastatin experienced an increase, atorvastatin-treated patients exhibited a reduction in apo AI (*P*=0.001).
Arca et al[38] Atorvastatin 10 mg daily, titrated to LDL-C goal, up to 80 mg daily for 24 weeks, following a 6-week dietary lead-in period vs fenofibrate 200 mg daily for 24 weeks, following a 6-week dietary lead-in period	OL, R Patients between 30 and 75 years old with diagnosis of familial combined hyper-lipidemia with TC and/or triglyceride levels ≥90th Italian population percentiles, and/or hyperapobeta-lipoproteinemia; patients were excluded if they had type III hyperlipidemia, were obese, had uncontrolled diabetes mellitus, or were taking lipid-lowering drugs	N=56 24 weeks	Primary: Change in TC, LDL-C, HDL-C, TG, apo A, endothelin-1 Secondary: Not reported	Primary: At 24 weeks, a greater percentage of patients on atorvastatin therapy was able to reach recommended lipid targets, compared to patients randomized to fenofibrate therapy (*P*=0.02). Atorvastatin therapy was associated with a significant 9% reduction in TC compared with fenofibrate therapy (95% CI, 3% to 15.1%; *P*=0.004). Atorvastatin therapy was associated with a significant 17% reduction in LDL-C compared with fenofibrate therapy (95% CI, 8% to 26.1%; *P*<0.001). Fenofibrate therapy was associated with a significant 15.5% reduction in TG compared with atorvastatin therapy (95% CI, 3.35% to 27.7%; *P*=0.013). Fenofibrate therapy was associated with a significant 14.2% increase in HDL-C compared with atorvastatin therapy (95% CI, 3.8% to 24.6%; *P*=0.008). Fenofibrate therapy was associated with a significant 5.2% and 22% increase in apo AI and apo AII compared with atorvastatin therapy (*P*=0.044 and *P*<0.001, respectively). Fenofibrate therapy was associated with a significant 16.7% reduction in endothelin-1 from baseline (*P*<0.05). Atorvastatin was not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				associated with a significant change in endothelin-1 (*P* value not reported). Secondary: Not reported
Hypercholesterolemia				
Lewis et al[39] Pravastatin 80 mg once daily vs placebo once daily	DB, MC, PC, RCT Adult patients ≥18 years of age with hypercholesterolemia, LDL-C ≥100 and TG <400 mg/dL, with at least 6-months history of compensated liver disease	N=326 36 weeks	Primary: Percent change from baseline at week 12 in LDL-C, TC, and TG, ALT event rate (ALT ≥2 times the ULN for those with normal ALT at baseline or a doubling of the baseline ALT for those with elevated ALT at baseline) Secondary: Not reported	Primary: Pravastatin was associated with a statistically significant reduction in LDL-C, TC, and TG at week-12 of the study compared to placebo (*P*<0.0001). There was no statistically significant difference between the two study groups in the ALT event rate at any time during the study (*P*>0.05). By the 36th week of the study, 7.5% of patients on pravastatin and 12.5% of patients taking placebo had at least one ALT event (*P*=0.1379). Secondary: Not reported
Stein et al[40] Rosuvastatin 40 mg daily for ≤96 weeks, after a 6-week dietary lead-in period	MC, OL Adult patients ≥18 years of age with LDL-C ≥190 and ≤260 mg/dL and TG <400 mg/dL; patients were excluded if they had homozygous familial hypercholesterolemia, significant liver enzyme	N=1,380 ≤96 weeks	Primary: Percentage of patients who achieved NCEP ATP III LDL-C goals (<160, <130, or <100 mg/dL) at 12 weeks Secondary: Reduction in LDL-C, HDL-C, apoliprotein	Primary: At 12 weeks, 83% of patients achieved the NCEP ATP III LDL-C goal (95% CI, 81% to 85%; *P* value not reported). Secondary: At 48 weeks, rosuvastatin therapy was associated with a significant reduction from baseline in LDL-C, apolipoprotein ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, TG, and apo B (*P*<0.0001). At 48 weeks, rosuvastatin therapy was associated with a significant increase from baseline in HDL-C (11%; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	elevations, active arterial disease within the previous 3 months, uncontrolled hyper-tension, serum CK >3 times ULN, serum creatinine >2.5 mg/dL, uncontrolled diabetes or hypothyroidism		ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, TG, and apo B	During the 96-week study period, 13% of patients experienced a serious adverse event, 0.4% of these patients died, and 2% of the patients experienced myalgia (*P* value not reported).
Meredith et al[41] Simvastatin 20 mg once daily vs simvastatin 80 mg once daily vs placebo once daily	DB, PG, RCT Patients who had undergone elective coronary angiography, had stable CAD, and an hsCRP >3 mg/L; patients were excluded if they had been hospitalized within 90 days with an ACS, had undergone a coronary revascularization procedure within 90 days, or if they had a known acute or long-term inflammatory process	N=107 16 weeks	Primary: Change in hsCRP from baseline Secondary: Change in LDL-C, TC, TG from baseline	Primary: There was no statistically significant difference between simvastatin 20 and 80 mg groups in terms of change in hsCRP from baseline (*P*=0.82). Secondary: Simvastatin, regardless of dose, was more effective than placebo in LDL-C reduction from baseline (*P*<0.001). Simvastatin, regardless of dose, was more effective than placebo in hsCRP reduction from baseline (*P*=0.007). Simvastatin, regardless of dose, was more effective than placebo in TC reduction from baseline (*P*<0.001). Simvastatin, regardless of dose, was more effective than placebo in triglyceride reduction from baseline (*P*=0.01).
Wolffenbuttel et al[42] CORALL Rosuvastatin 10 mg once daily for 6 weeks, after a 6-week dietary lead-in	MC, OL, PG, R Adult patients ≥18 years of age with type 2 diabetes for ≥3 month, LDL ≥3.36 mmol/L in statin naïve patients or	N=265 24 weeks	Primary: Reduction in LDL-C, HDL-C, apolipoprotein ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, TG, and apo	Primary: Both rosuvastatin and atorvastatin were associated with a significant reduction from baseline in LDL-C, apolipoprotein ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, TG, and apo B (*P*<0.001). Rosuvastatin therapy was associated with significant reduction in LDL-C (*P*<0.01), apolipoprotein ratio (*P*<0.05), LDL:HDL ratio

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
period, titrated to 20 mg daily for 6 weeks, titrated to 40 mg daily for 6 weeks vs atorvastatin 20 mg once daily for 6 weeks, after a 6-week dietary lead-in period, titrated to 40 mg daily for 6 weeks, titrated to 80 mg daily for 6 weeks	LDL between 2.99 mmol/L and 5.0 mmol/L in patients exposed to statin therapy within the previous 4 weeks, TG <4.52 mmol/L, and HbA_{1C}<10%		B, percentage of patients who achieved LDL-C goals (<2.6 mmol/L or <2.5 mmol/L) at 18 weeks Secondary: Not reported	(*P*<0.01), TC (*P*<0.05), TC:HDL ratio (*P*<0.05), non–HDL-C(*P*<0.05), and apo B (*P*<0.05), compared to atorvastatin therapy. Significantly greater percentage of patients randomized to rosuvastatin therapy achieved LDL-C goals at 18 weeks of therapy compared with the control (*P*<0.05). The incidence of treatment-related adverse events was similar in the rosuvastatin and atorvastatin groups (47% vs 50%, respectively; *P* value not reported). Secondary: Not reported
Deedwania, Gupta et al[43] IRIS Rosuvastatin 10 mg daily for 6 weeks, after a 6-week dietary lead-in period vs rosuvastatin 20 mg daily for 6 weeks, after a 6-week dietary lead-in period vs atorvastatin 10 mg daily for 6 weeks, after a 6-week dietary lead-in period vs	MC, OL, R South-Asian patients ≥18 years of age with CHD or CHD risk equivalent and LDL-C ≥100 mg/dL or ≥2 risk factors, 10-year CHD risk 10%-20%, and LDL-C ≥130 mg/dL or 0-1 risk factor and LDL-C ≥160 mg/dL, LDL-C had to be within 15% of each other and ≤300 mg/dL on 2 consecutive measurements, with TG <500 mg/dL	N=740 12 weeks	Primary: Percentage change in LDL-C from baseline at 6 weeks Secondary: Achievement of NCEP ATP III LDL-C goals, percentage change from baseline in non–HDL-C, HDL-C, TC, TG, and safety	Primary: At 6 weeks, patients randomized to the rosuvastatin 10 mg group experienced a significant reduction in LDL-C from baseline compared with atorvastatin 10 mg therapy (*P*=0.0023). The difference in LDL-C reduction from baseline at 6 weeks between the rosuvastatin 20 mg and atorvastatin 20 mg groups was not statistically significant (*P* value not reported). Secondary: The proportion of patients achieving NCEP ATP III LDL-C goals was similar in the rosuvastatin 10 mg and 20 mg and atorvastatin 10 mg and 20 mg groups (79%, 89%, 76%, and 85%, respectively). At 6 weeks, patients randomized to the rosuvastatin 10 mg group experienced a significant reduction in LDL-C:HDL-C ratio from baseline compared with atorvastatin 10 mg therapy (*P*<0.017). There were no clinically relevant differences between statins in adverse events or incidence of creatine kinase >10 times the ULN, ALT>3 times the ULN, proteinuria, or hematuria over a 6-week study period (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atorvastatin 20 mg daily for 6 weeks, after a 6-week dietary lead-in period				
Betteridge and Gibson[44] ANDROMEDA Rosuvastatin 10 mg daily for 8 weeks, after a 4-week washout period, titrated up to 20 mg daily for another 8 weeks vs atorvastatin 10 mg daily for 8 weeks, after a 4-week washout period, titrated up to 20 mg daily for another 8 weeks	DB, MC, PG, RCT Adult patients ≥18 years of age, with type 2 diabetes, with ≥2 FBG levels of ≥7.0 mmol/L, and a triglyceride level of ≤6.0 mmol/L; patients were excluded if they had type 1 diabetes, HbA_{1C} >9%, a history of cardiovascular disease or familial hypercholesterolemia, ALT/AST level ≥1.5 times the ULN, resting diastolic or systolic blood pressure >95 mmHg or >200 mmHg, respectively, or an unexplained serum CK level >3 times the ULN	N=509 16 weeks	Primary: Percentage changes from baseline in LDL-C levels at 16 weeks Secondary: Percentage changes from baseline in: LDL-C, TC, HDL-C, TG, non–HDL-C, cholesterol ratios, apo B, apolipoprotein ratio, HbA_{1C}, the proportion of patients achieving 2003 Joint European Societies LDL-C (<2.5 mmol/L) and TC (<4.5 mmol/L) goals	Primary: Rosuvastatin therapy was associated with a statistically significant reduction in LDL-C from baseline compared with atorvastatin therapy (57.4% vs 46%; *P*=0.001). Secondary: Rosuvastatin therapy was associated with a statistically significant reduction in apolipoprotein ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, and apo B from baseline compared with atorvastatin therapy (*P*<0.001). Rosuvastatin therapy was associated with a statistically significant reduction in HbA_{1C} from baseline compared with atorvastatin therapy (*P*=0.049). A higher percentage of patients randomized to rosuvastatin therapy were able to reach the 2003 Joint European Societies LDL-C goal compared to the atorvastatin group at 16 weeks of therapy (95.6% vs 87.3%; *P*=0.002). A higher percentage of patients randomized to rosuvastatin therapy were able to reach the 2003 Joint European Societies TC goal compared to the atorvastatin group at 16 weeks of therapy (93.4% vs 86%; *P*=0.01).
Betteridge, Gibson, Sager et al[45] Rosuvastatin 10 mg daily for 8 weeks, after a 4-week washout period, titrated up to 20 mg daily for another 8 weeks	DB, DD, MC, PG, RCT, SA of ANDROMEDA study Adult patients ≥18 years of age, with type 2 diabetes, with ≥2 FBG levels of ≥7.0	N=509 16 weeks	Primary: A composite end point of CRP <2mg/L and LDL-C <70 mg/dL Secondary: Not reported	Primary: Rosuvastatin therapy was associated with a statistically significant reduction in the primary end point from baseline compared with atorvastatin therapy (58% vs 37%; *P*<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs atorvastatin 10 mg daily for 8 weeks, after a 4-week washout period, titrated up to 20 mg daily for another 8 weeks	mmol/L, and a triglyceride level of ≤6.0 mmol/L (see above for exclusion criteria)			
Ferdinand et al[46] ARIES Rosuvastatin 10 mg one daily for 6 weeks, after a 6-week lead-in period vs rosuvastatin 20 mg once daily for 6 weeks, after a 6-week lead-in period vs atorvastatin 10 mg once daily for 6 weeks, after a 6-week lead-in period vs atorvastatin 20 mg once daily for 6 weeks, after a 6-week lead-in period	OL, R African-American adult patients ≥18 years of age with LDL ≥160 mg/dL but ≤300 mg/dL, TG <400. Patients were excluded if they had a history of homozygous familial hypercholesterolemia, type I, III, or V hypercholesterolemia, active arterial disease, uncontrolled hypertension, poorly controlled diabetes, active liver disease, transaminase elevation, bilirubin levels ≥2 times the ULN, unexplained serum creatine kinase levels >3 times the ULN, or serum creatinine 2.0 mg/dL.	N=774 6 weeks	Primary: The change from baseline in LDL-C at 6 weeks Secondary: Changes from baseline in other lipids, apolipoproteins	Primary: Patients in the rosuvastatin group experienced a statistically significant reduction in LDL-C levels compared to the atorvastatin groups (*P*<0.017). Secondary: Patients in the rosuvastatin group experienced a statistically significant reduction in TC, non–HDL-C levels, apo B concentrations, lipoprotein, and apolipoprotein ratios compared to the atorvastatin groups (*P*<0.017). Patients in the rosuvastatin group experienced a statistically significant increase in HDL-C levels compared to the atorvastatin groups (*P*<0.017). Side effects were similar in the rosuvastatin and atorvastatin treatment groups (34.4% and 33.6%, respectively; *P* value not reported).
Lloret et al[47]	MC, OL, RCT	N=696	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
STARSHIP Rosuvastatin 10 mg once daily for 6 weeks, after a 6-week lead-in period vs rosuvastatin 20 mg once daily for 6 weeks, after a 6-week lead-in period vs atorvastatin 10 mg once daily for 6 weeks, after a 6-week lead-in period vs atorvastatin 20 mg once daily for 6 weeks, after a 6-week lead-in period	Hispanic-American adult patients ≥18 years of age with a 10-year risk >10% for CHD, current CHD or its equivalent, LDL ≥130 mg/dL but ≤300 mg/dL on two measurements within 15% of each other, TG <400. Patients were excluded if they had a history of homozygous familial hypercholesterolemia, type I, III, or V hyper-cholesterolemia, active arterial disease, uncontrolled hypertension, poorly controlled diabetes, active liver disease, transaminase elevation, bilirubin levels ≥2 times the ULN, unexplained serum creatine kinase levels >3 times the ULN, or serum creatinine 2.0 mg/dL.	6 weeks	Percent change from baseline in LDL-C at 6 weeks Secondary: Proportion of patients reaching NCEP ATP III lipid goals, percent change from baseline in TC, apo B, non–HDL-C, TG, HDL, apo AI, LDL:HDL-C ratio, TC:HDL ratio, apo B:apo AI ratio, side effects at 6 weeks	Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in LDL-C from baseline compared to the atorvastatin 10 mg and 20 mg groups at 6 month (45%, 50%, 36%, and 42%, respectively; *P*<0.0001). Secondary: More patients randomized to the rosuvastatin 10 mg and 20 mg groups achieved NCEP ATP III LDL-C goals compared to the atorvastatin 10 mg and 20 mg groups at 6 month (78%, 88%, 60%, 73%, respectively; *P* value not reported). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in TC from baseline compared to the atorvastatin 10 mg and 20 mg groups at 6 month (*P*<0.0001, *P*<0.01, respectively). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in apo B from baseline compared to the atorvastatin 10 mg and 20 mg groups at 6 month (*P*<0.0001, *P*<0.017, respectively). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in LDL:HDL cholesterol ratio from baseline compared to the atorvastatin 10 mg and 20 mg groups, respectively, at 6 month (*P*<0.0001). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in TC:HDL cholesterol from baseline compared to the atorvastatin 10 mg and 20 mg groups at 6 month (*P*<0.0001, *P*<0.01, respectively). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in non-HDL:HDL cholesterol from baseline compared to the atorvastatin 10 mg and 20 mg groups at 6 month (*P*<0.0001, *P*<0.01, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in apo B:apo AI from baseline compared to the atorvastatin 10 mg and 20 mg groups, respectively, at 6 month (*P*<0.01). Side effects were similar across treatment groups (*P* value not reported). There were no cases of myopathy, rhabdomyolysis, or clinically significant increases in serum creatine kinase.
Insull et al[48] SOLAR Rosuvastatin 10 mg daily for 6 weeks, after a 6-week lead-in period, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved vs atorvastatin 10 mg for 6 weeks, after a 6-week lead-in period, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved vs	MC, RCT Patients were 18 years or older, enrolled in a managed care health plan, and classified as high risk by NCEP ATP III risk assessment. The NCEP ATP III defines high risk as the presence of CHD or CHD risk equivalents that consist of other clinical atherosclerotic disease, diabetes, or multiple CHD risk factors conferring a 10-year CHD risk of more than 20%; exclusion criteria included active vascular disease (such as unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular	N=1,632 12 weeks	Primary: Achievement of the NCEP ATP III high-risk LDL-C goal (<100 mg/dL) at week 6 Secondary: Proportions of patients who reached the high-risk LDL-C goal at 12 weeks, proportions of hypertriglyceridemic patients who achieved both the LDL-C goal (<100 mg/dL) and the non–HDL-C goal (<130 mg/dL) for high-risk patients, and changes in LDL-C and other lipid parameters at 6 and 12 weeks	Primary: Significantly greater proportion of patients randomized to rosuvastatin achieved their LDL-C target compared with the atorvastatin and simvastatin arms at 6 weeks of therapy (65%, 41%, and 39%, respectively; *P*<0.001). Secondary: After 12 weeks, 76% of patients taking rosuvastatin reached the LDL-C goal compared with 58% and 53% of patients on atorvastatin and simvastatin, respectively (*P*<0.001). After 6 weeks, 44% of hypertriglyceridemic patients taking rosuvastatin reached the combined LDL-C/non–HDL-C goals compared with 19% of patients on simvastatin, respectively (*P*<0.001). After 12 weeks, 57% of hypertriglyceridemic patients taking rosuvastatin reached the combined LDL-C/non–HDL-C goals compared with 31% of patients on simvastatin, respectively (*P*<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in LDL-C from baseline compared to the atorvastatin and simvastatin groups at 6 and 12 months (*P*<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in TC level from baseline compared to the atorvastatin and simvastatin groups at 6 and 12 months (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
simvastatin 20 mg for 6 weeks, after a 6-week lead-in period, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved	accident, CABG, or angioplasty within 3 months of study entry), uncontrolled hypertension, an FSG level of 180 mg/dL or higher or an HbA_{1c} level of ≥9%, active liver disease, unexplained serum CK elevation of more than 3 times the ULN, or a serum creatinine level of more than 2.0 mg/dL			Patients randomized to rosuvastatin experienced a statistically significant reduction in non–HDL-C level from baseline compared to the atorvastatin and simvastatin groups at 6 and 12 months (*P*<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in non–HDL-C:HDL-C ratio from baseline compared to the atorvastatin and simvastatin groups at 6 and 12 months (*P*<0.001). Patients randomized to rosuvastatin experienced a statistically significant increase in HDL-C from baseline compared to the atorvastatin and simvastatin groups at 12 months (*P*<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in TG from baseline compared to the simvastatin group at 6 and 12 months (*P*<0.001). The frequency and types of adverse events were similar in all treatment groups (*P* value not reported).
Leiter et al[49] POLARIS Rosuvastatin 40 mg once daily vs atorvastatin 80 mg once daily	DB, PG, R Patients between 45-80 years of age, with hypercholesterolemia and a history of CHD, clinical evidence of atherosclerosis, or a 10-year Framingham CHD-risk score >20%, with LDL-C ≥160 but <250 mg/dL, and TG <400 mg/dL	N=871 26 weeks	Primary: The percentage change from baseline in LDL-C levels at week 8 Secondary: Safety, the percentage change from baseline in LDL-C levels at week 26, the percentage change from baseline in other lipids and	Primary: Rosuvastatin 40 mg was associated with a significantly greater reduction in LDL-C from baseline at 8 weeks compared to atorvastatin 80 mg therapy (56% vs 52%; *P*<0.001). Secondary: Rosuvastatin 40 mg was associated with a significantly greater reduction in LDL-C from baseline at 26 weeks compared to atorvastatin 80 mg therapy (57% vs 53%; *P* value not reported). Rosuvastatin 40 mg was associated with a significantly greater reduction in TG (27% vs 22.2%; *P*<0.05), non–HDL-C (50.8% vs 48.3%; *P*<0.01), LDL-C:HDL-C ratio (58.5% vs 53.6%; *P*<0.001), TC:HDL-C (44.4% vs 41.1%; *P*<0.001), non–HDL-C:HDL-C (53.6% vs 49.6%; *P*<0.001), apo B (44.6% vs 42.3%; *P*<0.05), and apo AI

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			lipoproteins at weeks 8 and 26, and the proportion of patients reaching NCEP ATP III and 2003 European lipid goals at 8 and 26 weeks	(4.2% vs –0.5%; *P*<0.001) from baseline at 8 weeks compared to atorvastatin 80 mg therapy. Rosuvastatin 40 mg was associated with a significantly greater increase in HDL-C from baseline at 8 weeks compared to atorvastatin 80 mg therapy (9.6% vs 4.4%; *P*<0.001). At 6 weeks of therapy, more patients in the rosuvastatin 40 mg group achieved the NCEP ATP III LDL-C goal of <100 mg/dL compared with patients in the atorvastatin group (80% vs 72%; *P*<0.01). At 6 weeks of therapy, more patients in the rosuvastatin 40 mg group achieved NCEP ATP III LDL-C goal of <70 mg/dL compared with patients in the atorvastatin group (36 vs 18%; *P*<0.001). At 6 weeks of therapy, more patients in the rosuvastatin 40 mg group achieved the 2003 European lipid goals compared with patients in the atorvastatin group (79% vs 69%; *P*<0.001). The incidence of drug-related adverse effects was low in both rosuvastatin and atorvastatin treatment groups (0.5% vs 0.2%; *P* value not reported).
Jones et al[50] STELLAR Rosuvastatin once daily vs pravastatin once daily vs atorvastatin once daily	OL, PG Men and nonpregnant women ≥18 years of age with hypercholesterolemia, with LDL-C level ≥160 and <250 mg/dL at the 2 most recent consecutive visits	N=2,431 6 weeks	Primary: Percent change in LDL-C from baseline to 6 weeks Secondary: Percent change in HDL-C, triglyceride, and TC levels	Primary: Compared to all doses of atorvastatin and pravastatin, rosuvastatin was associated with a greater reduction in LDL-C from baseline (*P*<0.001 for both). When compared to baseline, the following changes in LDL-C were observed: a 45.8% to 55.0% reduction with rosuvastatin, a 36.8% to 51.1% reduction with atorvastatin, a 28.3% to 45.8% reduction with simvastatin, and a 20.1% to 29.7% reduction with pravastatin. The highest LDL reductions observed were a 55% reduction achieved in the rosuvastatin 40 mg group and a 51% reduction achieved in the atorvastatin 80 mg group (*P*=0.006).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs simvastatin once daily (treatments ranged from 10 mg to 80 mg)				Secondary: A 7.7% to 9.6% increase in HDL, a 19.8% to 26.1% reduction in TG, and a 32.9% to 40.2% reduction in TC was observed with rosuvastatin 10 mg to 40 mg group (*P* value not reported). A 2.1% to 5.7% increase in HDL, 20.0% to 28.2% reduction in TG, and a 27.1% to 38.9% reduction in TC was observed with the atorvastatin 10 mg to 80 mg group (*P* value not reported). A 5.2% to 6.8% increase in HDL, 11.9% to 18.2% reduction in TG, and a 20.3% to 32.9% reduction in TC was observed with the simvastatin 10 mg to 80 mg group (*P* value not reported). A 3.2% to 5.6% increase in HDL, 7.7% to 13.2% reduction in TG, and a 14.7% to 21.5% reduction in TC was observed with the pravastatin 10 mg to 40 mg group (*P* value not reported).
Stalenhoef et al[51] Rosuvastatin 10 mg daily for 6 weeks, titrated up to rosuvastatin 20 mg daily for another 6 weeks vs atorvastatin 10 mg daily for 6 weeks, titrated up to atorvastatin 20 mg daily for another 6 weeks vs placebo daily for 6 weeks, followed with rosuvastatin	DB, DD, MN, PG, RCT Men and women aged ≥18 years with metabolic syndrome (defined as at least 3 of the following: waist circumference >102 cm for men and >88 cm for women, TG ≥1.70 mmol/L, HDL-C <1.04 mmol/L for men and <1.30 mmol/L for women, BP ≥130/85 mm Hg or receiving antihypertensive therapy, FBG ≥6.11 mmol/L), LDL-C ≥3.36	N=401 12 weeks	Primary: Percentage change from baseline in LDL-C at 6 weeks Secondary: Percentage change from baseline in TC, LDL-C, HDL-C, non–HDL-C at 12 weeks	Primary: Rosuvastatin 10 mg reduced LDL-C significantly more than placebo (42.7% vs 0.3%, respectively; *P*<0.001) after 6 weeks of therapy. At 6 weeks, rosuvastatin had a significantly greater percentage change in LDL-C levels from baseline compared to atorvastatin (41.7% vs 35.7%, respectively; *P*<0.001). Secondary: At 12 weeks, significant reductions in LDL-C were observed in the rosuvastatin combined group in comparison to the atorvastatin group (48.9% vs 42.5%, respectively; *P*<0.001). Significantly more patients taking rosuvastatin achieved LDL-C goal (3.0 mmol/L) than patients taking atorvastatin at both 6 weeks (*P*<0.05) and 12 weeks (*P*<0.05). Percentage improvements in TC (*P*<0.001), HDL-C (*P*<0.01), and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
20 mg daily for another 6 weeks	mmol/L, and 10-year CHD risk score of >10%			non–HDL-C(*P*<0.001) from baseline were significantly greater in patients taking rosuvastatin compared to patients taking atorvastatin at both 6 and 12 weeks.
Ballantyne, Bertolami et al[52] MERCURY II Rosuvastatin 20 mg daily for 8 weeks after a 6-week dietary lead-in period vs atorvastatin 10 mg daily for 8 weeks after a 6-week dietary lead-in period vs atorvastatin 20 mg daily for 8 weeks after a 6-week dietary lead-in period vs simvastatin 20 mg daily for 8 weeks after a 6-week dietary lead-in period vs simvastatin 40 mg daily for 8 weeks after a 6-week dietary lead-in period	MC, OL, R Patients ≥18 years of age, at high risk for CHD events, fasting LDL-C level ≥130 to <250 mg/dL on two separate measurements within 15% of each other, and a fasting TG <400 mg/dL; patients were excluded if were pregnant, lactating, had a history of homozygous familial hypercholesterolemia, hyperlipoproteinemia types I, III, IV, or V, unstable arterial disease within 3 months, uncontrolled hypertension, FSG >180 mg/dL, active liver disease, serum creatinine >2 mg/dL or unexplained serum creatine kinase levels >3 times the ULN	N=1,993 16 weeks	Primary: The proportion of patients achieving LDL-C<100 mg/dL at week 16 Secondary: The proportion of patients meeting the LDL-C target at week 8, change in lipid and lipoprotein measures at weeks 8 and 16, adverse events	Primary: At 16 weeks, more patients randomized to rosuvastatin therapy were able to achieve LDL-C target level <100 mg/dL compared to patients who received atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and simvastatin 40 mg for the duration of the study (83%, 42%, 64%, 32%, and 56%, respectively; *P* value not reported). At 16 weeks, significantly more patients who switched to rosuvastatin therapy achieved LDL-C target level <100 mg/dL compared to patients who remained on their initial medication regimen (*P*<0.001). Secondary: At 16 weeks, patients who switched to rosuvastatin therapy experienced a significant LDL-C reduction from baseline compared to patients remaining on their initial medication regimen (*P*<0.001). At 8 weeks, significantly more patients randomized to rosuvastatin therapy were able to achieve LDL-C target level <100 mg/dL compared to patients who received atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and simvastatin 40 mg (82%, 43%, 62%, 33%, and 55%, respectively; *P*<0.0001). At 16 weeks, significantly more patients randomized to rosuvastatin therapy were able to achieve LDL-C level <70 mg/dL compared to patients who received atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and simvastatin 40 mg (37%, 7%, 13%, 1%, and 10%, respectively; *P* value not reported). At 16 weeks, patients who switched to rosuvastatin therapy experienced a significant atherogenic lipid measure and ratio reduction from baseline compared to patients remaining on their initial medication regimen (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
After 8 weeks of treatment, patients received an additional 8 weeks of either initial or rosuvastatin therapy.				At 16 weeks, significantly more hypertriglyceridemic patients randomized to rosuvastatin therapy were able to achieve LDL-C target level <100 mg/dL and non–HDL-C targets compared to patients who received atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and simvastatin 40 mg (80%, 20%, 42%, 19%, and 29%, respectively; *P* value not reported). The frequency and type of adverse events were similar in all treatment groups (*P* value not reported). In addition, there were no symptomatic adverse events associated with hepatic dysfunction.
Rogers et al[53] Simvastatin 10, 20, 40, or 80 mg daily vs atorvastatin 10, 20, 40, or 80 mg daily	MA Randomized, comparative studies comparing atorvastatin with simvastatin in patients >18 years of age with elevated levels of serum TC and LDL-C; studies were excluded if they involved animals, had a crossover, dose-titration, or forced dose-titration design, or did not include a washout period of previous statin or other lipid-lowering therapy	N=8,320 (18 studies) Up to 12 weeks	Primary: Reductions in TC, LDL-C, TG and increases in HDL-C Secondary: Not reported	Primary: Simvastatin appeared to be comparable to atorvastatin in terms of TC reduction from baseline at 4 times the dose of atorvastatin (*P*>0.05). Simvastatin 20 mg and 40 mg were less effective at reducing LDL-C level from baseline compared to atorvastatin 40 mg and 80 mg, respectively (*P*<0.001). Simvastatin, dosed 40 mg to 80 mg, was comparable to atorvastatin 20 mg in terms of triglyceride reduction from baseline (*P*=0.22 and *P*=0.53, respectively). Atorvastatin, dosed 40 mg to 80 mg, was more effective in reducing triglyceride level from baseline compared to all simvastatin doses studied (*P*<0.001). Simvastatin 10 mg, 20 mg, and 80 mg were more effective than atorvastatin 80 mg in increasing HDL-C from baseline (*P*<0.05). Secondary: Not reported
Milionis et al[54] ATOROS	OL, PG, R Patients, average age of	N=180 24 weeks	Primary: Percentage of patients achieving the	Primary: At 6 weeks, 75% and 71.7% of patients achieved the NCEP ATP III LDL-C goal with rosuvastatin and atorvastatin therapies, respectively

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rosuvastatin 10 mg once daily for 6 weeks, after a 6-week dietary lead-in period, titrated to 20 mg daily for 18 weeks vs atorvastatin 20 mg once daily for 6 weeks, after a 6-week dietary lead-in period, titrated to 40 mg daily for 18 weeks	53.6 years, free of symptomatic ischemic heart disease or any other clinically evident heart disease, at moderate risk for CHD according to NCEP ATP classification, with baseline TC >240 mg/dL, and TG <350 mg/dL; patients were excluded if they had abnormal liver function tests, impaired renal function, diabetes, elevated thyroid-stimulating hormone, or any other condition potentially interfering with successful completion of study protocol; a control group of healthy volunteers was included in the analysis		NCEP ATP III LDL-C goal (<130 mg/dL) Secondary: Change from baseline in LDL-C, HDL-C, TC, TG, non-HDL, and apo B at 24 weeks	(*P* value not reported). Secondary: Both rosuvastatin and atorvastatin were associated with statistically significant reductions in LDL from baseline (48.7% vs 44.6%; *P*<0.001). Rosuvastatin therapy was associated with a significant 5% increase from baseline in HDL-C (*P*<0.001). Atorvastatin therapy was associated with a significant 2.1% reduction from baseline in HDL-C (*P*<0.001). Compared to atorvastatin, rosuvastatin was associated with a significantly greater increase in HDL-C (*P*=0.002). Both rosuvastatin and atorvastatin were associated with statistically significant reductions in TC from baseline (36.1% vs 36.9%; *P*<0.001). Both rosuvastatin and atorvastatin were associated with statistically significant reductions in TG from baseline (29% vs 27.8%; *P*<0.001). Both rosuvastatin and atorvastatin were associated with statistically significant reductions in non-HDL from baseline (45% vs 46%; *P*<0.001). Both rosuvastatin and atorvastatin were associated with statistically significant reductions in apo B from baseline (29% vs 26%; *P*<0.001). The incidence of myalgia was similar in both treatment groups (3 %; *P* value not reported). There were no reports of significant ALT or CK elevations.
Clearfield et al[55] PULSAR Rosuvastatin 10 mg once daily for 6 weeks	OL, PG, R, MC Patients ≥18 years of age with hypercholesterolemia and either a history of	N=996 6 weeks	Primary: Percentage change from baseline in LDL-C at 6 weeks Secondary:	Primary: Compared to atorvastatin, rosuvastatin was associated with a statistically greater reduction from baseline in LDL-C at 6 weeks (42.7% vs 44.6%; *P*<0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs atorvastatin 20 mg once daily for 6 weeks	CHD or a CHD-risk equivalent, with the mean of the two most recent LDL levels (within 15% of each other) ≥130 mg/dL and <220 mg/dL, as well as TG <400 mg/dL; patients were excluded if they had an MI, unstable angina, myocardial revascularization, a TIA, or stroke within 8–12 weeks of study onset, had a history of statin-induced myopathy, were awaiting a planned myocardial revascularization, had CHF NYHA class III-IV, a history of malignancy, homozygous FH, current active liver disease, unexplained CK elevation ≥3 the ULN, serum creatinine >2.0 mg/dL, uncontrolled, alcohol or drug abuse within the last 5 years, hormone-replacement therapy or oral contraceptives		Percentage of patients achieving the NCEP ATP III and the 2003 European LDL-C goals (<100 mg/dL), the 2003 European LDL-C goal for patients at greatest risk (CVD, diabetes, LDL-C ≥6mmol/L, TC ≥8 mmol/L, or blood pressure ≥180/110 mm Hg), the NCEP ATP III non-HDL-C goal (<130 mg/dL, combined LDL-C:TC goal <175-190 mg/dL, the percentage change from baseline in HDL-C, TC, TG, non-HDL-C, apo B, LDL-C:HDL-C, TC:HDL-C, non-HDL-C:HDL-C, lipoprotein(a) frequency and severity of adverse events	Significantly more patients in the rosuvastatin group achieved NCEP ATP III and the 2003 European LDL-C goals, compared with the atorvastatin-treated group (68% vs 63%; *P*<0.05). In addition, more rosuvastatin-treated patients at greatest risk for CHD reached the 2003 European LDL-C goals, compared to patients treated with atorvastatin (65.6% vs 60.3%; *P*>0.05). While more patients reached the NCEP ATP III non–HDL-C goal with rosuvastatin compared with atorvastatin, the difference was not statistically significant (69.7% vs 65%; *P*>0.05). While more patients reached the NCEP ATP III combined LDL-C:TC goal with rosuvastatin compared with atorvastatin, the difference was not statistically significant (55.2% vs 53.3%; *P*>0.05). Rosuvastatin was associated with a statistically significant increase in HDL-C from baseline compared to atorvastatin (6.4% vs 3.1%; *P*<0.001). There was no statistically significant difference in the change from baseline in TC, TG, non–HDL-C, and apo B observed with rosuvastatin and atorvastatin (*P*>0.05). Rosuvastatin was associated with a statistically significant reduction in LDL-C:HDL-C from baseline compared to atorvastatin (47.6% vs 44%; *P*<0.001). Rosuvastatin was associated with a statistically significant reduction in TC:HDL-C from baseline compared to atorvastatin (34.6% vs 32.3%; *P*<0.01). Rosuvastatin was associated with a statistically significant reduction in non-HDL-C:HDL-C from baseline compared to atorvastatin (43.3% vs 40.2%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	within 3 months of study onset			Atorvastatin was associated with a statistically significant increase in lipoprotein(a) from baseline compared to rosuvastatin (13.3% vs 2.1%; *P*<0.001). The frequency and type of adverse events were similar with the rosuvastatin and atorvastatin groups (27.5% vs 26.1%; *P* value not reported). The most commonly reported adverse effects were myalgia and urinary tract infections.
Bullano, Kamat et al[56] Rosuvastatin (11 mg mean daily dose) vs atorvastatin (15 mg mean daily dose)	RETRO Patients ≥18 years of age, initiated on rosuvastatin or atorvastatin between August 1, 2003 and September 30, 2004 with at least one lipid level (LDL-C, TG, HDL-C, TC) obtained prior to and posttherapy initiation	N=453 Up to 79 days of therapy	Primary: Percentage change from baseline in LDL-C Secondary: Percentage of patients achieving the NCEP ATP III LDL-C goals (<100 mg/dL), the percentage change from baseline in HDL-C, TC, TG, non-HD-CL	Primary: Patients treated with rosuvastatin experienced a statistically greater percent reduction in LDL-C from baseline compared with the atorvastatin-treated group (35% vs 26%; *P*<0.001). Secondary: Significantly more patients in the rosuvastatin group achieved NCEP ATP III LDL-C goals, compared with the atorvastatin-treated group, when adjusted for age, sex, LDL-lowering required to reach goal, risk category, and duration of therapy (74% vs 65%; *P*<0.05). Unadjusted attainment rates were similar in both treatment groups (*P*=0.088). Moreover, patients in the rosuvastatin group required greater LDL-C reduction to reach their LDL goal compared to patients treated with atorvastatin (26.3% vs 23.5%; *P*<0.05). In addition, significantly more patients in the rosuvastatin groups reached the updated, optional NCEP ATP III LDL-C goals, compared to atorvastatin group (61% vs 48%; *P*<0.05). There was no statistically significant difference between the change in HDL-C obtained with rosuvastatin and atorvastatin (*P*=0.234). Patients treated with rosuvastatin experienced a statistically greater percent reduction in TC from baseline compared with the atorvastatin-treated group (26% vs 20%; *P*<0.001). There was no statistically significant difference between the TG reduction obtained with rosuvastatin and atorvastatin (*P*=0.192).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patients treated with rosuvastatin experienced a statistically greater percent reduction in non–HDL-C from baseline compared with the atorvastatin-treated group (33% vs 25%; *P*<0.001).
Bullano, Wertz et al[57] Rosuvastatin 5-40 mg daily vs other statins (atorvastatin 10-80 mg/day, simvastatin 5-80 mg/day, pravastatin 10-80 mg/day, lovastatin 10-80 mg/day, fluvastatin 20-160 mg/day)	RETRO Patients ≥18 years of age, initiated on a statin between August 1, 2003 and September 30, 2004 with at least one LDL-C level obtained prior to and after therapy initiation	N=8,251 Up to 122 days of therapy	Primary: Percentage change from baseline in LDL-C Secondary: Percentage of patients achieving the NCEP ATP III LDL-C goals (<100 mg/dL), the percentage change from baseline in HDL-C, TC, and TG	Primary: Patients treated with rosuvastatin experienced a statistically greater percent reduction in LDL-C from baseline compared with other statin groups (33% vs atorvastatin 24%, simvastatin 20%, pravastatin 18%, fluvastatin 13% and lovastatin 16%; *P*<0.05). Moreover, rosuvastatin 10 mg was associated with a greater percentage of LDL-C reduction from baseline compared to either atorvastatin 10-20 mg (*P*<0.05) or simvastatin 10-20 mg (*P*<0.05). Secondary: Significantly more patients in the rosuvastatin group achieved NCEP ATP III LDL-C goals, compared with the other statin treatment groups (*P*<0.05). Moreover, patients in the rosuvastatin group required greater LDL-C reduction to reach their LDL goal compared to patients treated with other statins (29% vs 23-27%; *P*<0.05). In addition, significantly more patients in the rosuvastatin groups reached the updated, optional NCEP ATP III LDL-C goals, compared to other statins (58% vs 29-48%; *P*<0.05). There was no statistically significant difference between the HDL-C reduction obtained with rosuvastatin and other statins (*P*>0.05). Patients treated with rosuvastatin experienced a statistically greater percent reduction in total cholesterol from baseline compared with other statin groups (24% vs atorvastatin 18%, simvastatin 14%, pravastatin 13%, fluvastatin 10%, and lovastatin 12%; *P*<0.05). Patients treated with rosuvastatin experienced a statistically greater percent reduction in TG from baseline compared with other statin groups (11% vs simvastatin 6%, pravastatin 4%, fluvastatin 4%, and lovastatin 5%; *P*<0.05). However there was no statistically significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				difference in TG reduction from baseline between rosuvastatin and atorvastatin-treated groups (11% vs 10%; *P*>0.05).
Ai et al[58] STELLAR Rosuvastatin 40 mg daily for 6 weeks vs atorvastatin 80 mg daily for 6 weeks	OL Patients ≥18 years of age, with hypercholesterolemia, with LDL-C levels ≥160 mg/dL and <250 mg/dL, as well as TG <400 mg/dL	N=271 6 weeks	Primary: Change in direct LDL-C and small dense LDL-C Secondary: Percentage change from baseline in HDL-C, TC, TG, non-HDL-C, TC:HDL-C ratio	Primary: Rosuvastatin was associated with a significant reduction from baseline in direct LDL-C compared with atorvastatin (52% vs 50%; *P*=0.01). Rosuvastatin was associated with a significant reduction from baseline in small dense LDL-C compared with atorvastatin (53% vs 46%; *P*<0.001). Secondary: Rosuvastatin was associated with a significant increase from baseline in HDL-C compared with atorvastatin (10% vs 2%; *P*<0.001). There was no statistically significant difference between the TC reduction obtained with rosuvastatin and atorvastatin (*P*=0.10). There was no statistically significant difference between the TG reduction obtained with rosuvastatin and atorvastatin (*P*=0.50). Rosuvastatin was associated with a significant reduction from baseline in non–HDL-C compared with atorvastatin (51% vs 48%; *P*<0.0078). Rosuvastatin was associated with a significant reduction from baseline in TC:HDL-C compared with atorvastatin (46% vs 39%; *P*<0.001).
Fox, Gandhi, Ohsfeldt, Blasetto et al[59] Rosuvastatin at an average dose of 11.7 mg vs other statins (atorvastatin, pravastatin, lovastatin,	RETRO Adult patients with diabetes (ICD 9 code 250, on antidiabetic medication, or FBG >126 mg/dL), newly prescribed a statin between August 2003 and March 2006	N=4,754 Patients received statin therapy between August 2003 and March 2006	Primary: Percent reduction in LDL-C from baseline, percentage of patients achieving LDL-C goal <100 mg/dL Secondary: Not reported	Primary: Rosuvastatin was associated with a significant reduction from baseline in small dense LDL-C compared with atorvastatin (22.5%), simvastatin (20.1%), pravastatin (13.7%), lovastatin (17.3%), and fluvastatin (15.8%) (*P*<0.0001). Compared to other statins, a greater percentage of patients receiving rosuvastatin were able to reach their LDL-C goal <100 mg/dL (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
simvastatin, fluvastatin) dosed 17-64 mg				Secondary: Not reported
Harley et al[60] Rosuvastatin after simvastatin therapy (5-80 mg) vs atorvastatin after simvastatin therapy (5-80 mg) vs lovastatin after simvastatin monotherapy (5-80 mg) vs pravastatin after simvastatin monotherapy (5-80 mg) vs fluvastatin after simvastatin monotherapy (5-80 mg) vs simvastatin in combination with ezetimibe after simvastatin monotherapy	RETRO Adult patients ≥18 years of age, receiving simvastatin monotherapy between July 2005 and June 2006, switched to other statin therapy	N=134,160 1 year	Primary: Percentage of patients achieving NCEP ATP III LDL goal after switching from simvastatin to another statin Secondary: Not reported	Primary: Of those patients not at NCEP ATP III LDL goal with simvastatin monotherapy, 73% reached their LDL goal following the switch to another statin (*P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(5-80 mg)				
Fox, Gandhi, Ohsfeldt, and Davidson [61] Rosuvastatin switch vs simvastatin switch	RETRO Adult patients ≥18 years of age switching to either rosuvastatin or simvastatin from another statin between August 2003 and March 2006, not receiving other antidyslipidemic medications in the 12 months before or after initiating statin therapy	N=277 Patients received statin therapy between August 2003 and March 2006	Primary: Percent reduction in LDL-C from baseline Secondary: Not reported	Primary: Patients switched to rosuvastatin experienced a significant reduction in LDL-C from baseline compared to simvastatin-treated patients (18.5% vs 5.8%; *P*<0.05). LDL-C reduction of >25% was achieved by a significantly greater percentage of patients switched to rosuvastatin therapy than those switched to simvastatin therapy (44% vs 29%; *P*<0.05). Patients switched from atorvastatin to rosuvastatin experienced a significantly greater reduction in LDL-C from baseline compared to those switched to simvastatin therapy (14.6% vs 4.6%; *P*<0.05). Secondary: Not reported
Piorkowski et al[62] Atorvastatin 40 mg once daily vs atorvastatin 10 mg once daily in addition to ezetimibe 10 mg daily, separate entities	RCT Patients between 18 and 80 years of age with clinically stable angiographically documented CHD and LDL-C >2.5 mmol/L despite ongoing atorvastatin 10-20 mg daily, receiving aspirin and clopidogrel; patients were excluded if they had a history of an MI or CK elevation within the last 4 weeks, recent warfarin treatment, tumors, severe renal	N=56 4 weeks	Primary: Change in liver transaminases, CK, HDL, LDL, and TG from baseline, percentage of patients achieving the ATP III LDL-C goal (≤2.5 mmol/L) Secondary: Not reported	Primary: There were no statistically significant differences from baseline in liver transaminases, CK, or HDL in either group (*P* value not reported). Both groups exhibited a statistically significant reduction in LDL-C from baseline (*P*<0.005). There was no statistically significant difference between the two groups in degree of LDL-C reduction from baseline (*P* value not reported). Both the atorvastatin 40 mg and the combination therapy groups exhibited a statistically significant reduction in triglyceride level from baseline (*P*<0.005 and *P*<0.05, respectively). There was no statistically significant difference between the two groups in the percentage of patients achieving the ATP III LDL-C goal (≤2.5 mmol/L) (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	insufficiency, active liver disease, liver cirrhosis, unexplained transaminase elevation, recent antibiotic therapy, or known alcohol abuse			Secondary: Not reported
Constance et al[63] Atorvastatin 20 mg daily for 6 weeks, following a 4-week atorvastatin 10 mg run-in period vs ezetimibe 10 mg daily added to simvastatin 20 mg daily, separate entities, for 6 weeks, following a 4-week atorvastatin 10 mg run-in period vs ezetimibe 10 mg daily added to simvastatin 40 mg daily, separate entities, for 6 weeks, following a 4-week atorvastatin 10 mg run-in period	DB, MC, PG, RCT Patients ≥18 years of age, with type 2 diabetes, HbA_{1C} ≤10%, ALT/AST levels <1.5 times the ULN, CK <1.5 times the ULN; patients were excluded if they had congestive heart failure New York Heart Association classes III- IV, MI, CABG or angioplasty within 3 months, uncontrolled hypertension or endocrine/metabolic disease, renal dysfunction or nephrotic syndrome, alcohol consumption >14 drinks per week and treatment with excluded concomitant medications	N=661 6 weeks	Primary: Change from baseline in LDL-C at 6 weeks Secondary: Change from baseline in TC, HDL-C, TG, non–HDL-C, apo B, LDL-C:HDL-C ratio, and TC:HDL-C ratio	Primary: Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the atorvastatin 20 mg monotherapy group (P≤0.001). Secondary: Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant reduction from baseline in TC, non-HDL, apo B, LDL-C:HDL-C ratio, and TC:HDL-C ratio compared with the atorvastatin 20 mg monotherapy group (P≤0.001). Patients on the ezetimibe/simvastatin 10/40 mg combination therapy experienced a statistically significant reduction in CRP from baseline compared with the atorvastatin 20 mg monotherapy group (P=0.006). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin 10/20 mg and 10/40 mg combination therapy achieved LDL-C <2.5 mmol/L, compared to the atorvastatin 20 mg group (90.5%, 87%, and 70.4%, respectively; P≤0.001). The incidence of drug-related adverse effects was similar in the ezetimibe/simvastatin 10/20 mg and 10/40 mg combination therapy and atorvastatin monotherapy groups (0.5%, 0.5%, and 2.3%, respectively; P value not reported).
Pearson et al[64]	MA	N=4,373 (4 studies)	Primary: Change from baseline	Primary: Across all doses, patients on the ezetimibe/simvastatin combination

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Atorvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 6 weeks vs simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 12 weeks vs ezetimibe 10 mg daily for 12 weeks vs ezetimibe 10 mg daily added to simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily, separate entities, for up to 12 weeks vs placebo for 12 weeks	Three identical, prospective 12-week studies randomizing patients to placebo, ezetimibe, ezetimibe with simvastatin or simvastatin alone, and one phase III double-blind, active-controlled study allocating patients to ezetimibe/simvastatin or atorvastatin for 6 weeks	up to 12 weeks	in LDL-C level, CRP, proportion of patients reaching LDL-C target (<100 mg/dL or <70 mg/dL) Secondary: Not reported	therapy experienced a statistically significant LDL-C reduction from baseline compared with the simvastatin monotherapy group (52.5% vs 38%; *P*<0.001). Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the atorvastatin monotherapy group (53.4% vs 45.3%; *P*<0.001). Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant CRP reduction from baseline compared with the simvastatin monotherapy group (31% vs 14.3%; *P*<0.001). Patients on the ezetimibe/simvastatin combination therapy experienced a similar CRP reduction from baseline compared with the atorvastatin monotherapy group (25.1% vs 24.8%; *P* value not reported). The reduction in CRP from baseline was not significantly different between simvastatin 10 mg and placebo groups (*P*>0.10). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <100 mg/dL, compared to the simvastatin group (78.9% vs 43.1%; *P*<0.001). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin group (37% vs 5.7%; *P*<0.001). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <100 mg/dL, compared to the atorvastatin group (79.8% vs 61.9%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Significantly greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the atorvastatin group (36.2% vs 16.8%; *P*<0.001). Secondary: Not reported
Goldberg et al[65] VYTAL Atorvastatin 10 mg daily vs atorvastatin 20 mg daily vs atorvastatin 40 mg daily vs simvastatin 20 mg daily, in addition to ezetimibe 10 mg daily, separate entities vs simvastatin 40 mg daily, in addition to ezetimibe 10 mg daily, separate entities	DB, MC, PG, RCT Adult patients with type 2 diabetes between 18 and 80 years of age with HbA_{1c} ≤8.5%, LDL-C >100 mg/dL and a triglyceride level <400 mg/dL	N=1,229 6 weeks	Primary: Percent reduction in LDL-C level at week 6 Secondary: Proportion of patients who achieved the NCEP ATP III LDL-C goal (<70 mg/dL), proportion of patients who achieved LDL-C level of <100 mg/dl, percent change from baseline in HDL-C, non–HDL-C, TC, TG, and CRP	Primary: Patients randomized to simvastatin 20 mg/ezetimibe 10 mg combination therapy experienced a greater reduction in LDL-C from baseline at week 6 of the study compared to patients receiving atorvastatin 10 mg or 20 mg daily (53.6%, 38.3%, and 44.6%, respectively; *P*<0.001). Patients randomized to simvastatin 40 mg/ezetimibe 10 mg combination therapy experienced a greater reduction in LDL-C from baseline at week 6 of the study compared to patients receiving atorvastatin 40 mg daily (57.6% and 50.9%, respectively; *P*<0.001). Secondary: A greater proportion of patients randomized to simvastatin 20 mg/ezetimibe 10 mg combination therapy achieved LDL-C<70 mg/dL compared to patients receiving atorvastatin 10 mg or 20 mg daily (59.7%, 21.5%, and 35%, respectively; *P*<0.001). A greater proportion of patients randomized to simvastatin 40 mg/ezetimibe 10 mg therapy achieved LDL-C<70 mg/dL compared to patients receiving atorvastatin 40 mg daily (74.4% and 55.2%, respectively; *P*<0.001). A greater proportion of patients randomized to simvastatin 20 mg/ezetimibe 10 mg therapy achieved LDL-C<100 mg/dL compared to patients receiving atorvastatin 10 mg or 20 mg daily (90.3%, 70%, and 82.1%, respectively; *P*=0.007).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				A greater proportion of patients randomized to simvastatin 40 mg/ezetimibe 10 mg therapy achieved LDL-C<100 mg/dL compared to patients receiving atorvastatin 40 mg daily (93.4% and 88.8%, respectively; *P*=0.07). Patients randomized to simvastatin/ezetimibe combination therapy, at all doses, experienced a significant increase in HDL level (*P*≤0.001), a greater reduction in TC, and non–HDL-C (*P*<0.001) compared to patients receiving atorvastatin, at all doses. Patients randomized to simvastatin 20 mg/ezetimibe 10 mg combination therapy experienced a significant reduction in CRP and triglyceride level compared to patients receiving atorvastatin (*P*=0.02). Side effects were similar in the simvastatin/ezetimibe and atorvastatin groups (19.85 vs 22.7%; *P* value not reported).
Ballantyne, Weiss et al[66] EXPLORER Rosuvastatin 40 mg daily for 6 weeks vs ezetimibe 10 mg, in addition to rosuvastatin 40 mg daily, separate entities, for 6 weeks	MC, OL, PG, RCT Patients ≥18 years of age with primary hypercholesterolemia and CHD or clinical evidence of atherosclerosis or a CHD risk equivalent (10-year CHD risk score >20%), and mean LDL-C between 160 mg/dL and 250 mg/dL with the two last measurements within 15% of each other, and TG <400 mg/dL; patients were excluded if they were women on	N=469 6 weeks	Primary: Percentage of patients achieving the ATP III LDL-C goal (<100 mg/dL) at 6 weeks Secondary: Change from baseline in LDL-C, TC, non–HDL-C, TG, LDL:HDL cholesterol, TC:HDL, non-HDL/HDL, apo B, CRP, HDL, apo AI, adverse effects	Primary: Significantly greater proportion of patients randomized to the combination therapy achieved their ATP III LDL-C goal compared to the monotherapy group (94% vs 79.1%; *P*<0.001). Secondary: Patients on the combination therapy experienced a significantly greater reduction from baseline in LDL-C compared to the monotherapy group (70% vs 57%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in TC compared to the monotherapy group (51% vs 42%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in non–HDL-C compared to the monotherapy group (65% vs 52%; *P*<0.001). Patients on the combination therapy experienced a significantly greater

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	hormonal therapy, taking statins within 6 weeks, potent CYP3A4 inhibitors within 5 weeks, oral corticosteroids started within 6 weeks or verapamil within 4 days of study onset; patients were also excluded if they had ALT/AST or creatine kinase >1.5 times the ULN, poorly controlled, newly diagnosed diabetes type 1 or 2, or had changed their antidiabetic therapy within 3 months of baseline, had uncontrolled hypertension, or body mass index ≥30 kg/m^2			reduction from baseline in TG compared to the monotherapy group (35% vs 25%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in LDL:HDL cholesterol compared to the monotherapy group (72% vs 60%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in TC:HDL cholesterol compared to the monotherapy group (56% vs 45%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in non-HDL/HDL cholesterol compared to the monotherapy group (67% vs 55%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in apo B compared to the monotherapy group (56% vs 45%; *P*<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in CRP compared to the monotherapy group (46% vs 29%; *P*<0.001). There was no statistically significant difference in HDL-C increase (*P*=0.151) or apo AI reduction (*P*=0.202) between the combination therapy and rosuvastatin monotherapy groups. The frequency and types of adverse events were similar across the combination and monotherapy groups (31.5% and 33.5%, respectively; *P* value not reported).
Ose et al[67] Simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 14 weeks	DB, MC, RCT Extension of a 12-week study in patients, aged 22 to 83 years, with	N=1,037 14 weeks	Primary: Change from baseline in LDL-C level, TG, TC, non-HDL, CRP, LDL:HDL	Primary: Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the simvastatin monotherapy group (53.7% vs 38.8%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ezetimibe 10 mg daily added to simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily, separate entities, for 14 weeks vs ezetimibe 10 mg once daily for 14 weeks vs placebo once daily for 14 weeks	primary hyper-cholesterolemia (LDL-C between 145 mg/dL and 250 mg/dL and TG <350 mg/dL) who were randomized to ezetimibe/simvastatin 10/10, 10/20, 10/40 or 10/80 mg combination tablet, simvastatin 10, 20, 40, or 80 mg monotherapy, ezetimibe 10 mg, or placebo		cholesterol ratio, TC:HDL ratio, proportion of patients reaching LDL-C target (<100 mg/dL, or <70 mg/dL) Secondary: Not reported	Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant reduction from baseline in TG, TC, non-HDL, CRP, LDL:HDL cholesterol ratio, and TC:HDL ratio compared with the simvastatin monotherapy group (*P*<0.001). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <100 mg/dL, compared to the simvastatin group (79.2% vs 47.9%; *P*<0.001). A greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin group (30.4% vs 7%; *P*<0.001). The incidence of drug-related adverse effects was similar in the ezetimibe/simvastatin and simvastatin monotherapy groups (7.4% vs 5.5%, respectively; *P* value not reported). Secondary: Not reported
Patel et al[68] Simvastatin 20 mg, in addition to placebo for 6 weeks vs ezetimibe 10 mg, in addition to simvastatin 20 mg, separate entities, for 6 weeks	DB, MC, PG, RCT Patients 18-75 years of age with primary hypercholesterolemia and CHD (at least 3 months prior to baseline), not on lipid management therapy; patients were excluded if they were women on hormonal therapy, taking statins within 6 weeks, potent CYP3A4	N=153 6 weeks	Primary: Mean change from baseline in LDL-C level, proportion of patients who reached LDL-C target (<3 mmol/l) at 6 weeks Secondary: Change in serum cholesterol, TG, HDL	Primary: Patients on the combination therapy experienced an additional LDL-C reduction of 14.6% compared to the simvastatin monotherapy group (95% CI, 10.1 to 19.1; *P*<0.0001). Significantly greater proportion of patients randomized to the combination therapy achieved their LDL-C goal compared to the monotherapy group (93% vs 75%, respectively; *P*<0.001). Patients on combination therapy were 5.1 times more likely to reach target LDL-C levels compared to patients on simvastatin alone (95% CI, 1.8 to 15.0; *P*=0.003). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	inhibitors within 5 weeks, oral corticosteroids started within 6 weeks or verapamil within 4 days of study onset; patients were also excluded if they had ALT/AST or creatine kinase >1.5 times the ULN, poorly controlled, newly diagnosed diabetes type 1 or 2, or had changed their antidiabetic therapy within 3 months of baseline, had uncontrolled hypertension, or body mass index ≥30 kg/m^2			Patients on the combination therapy experienced an additional TC reduction of 0.69 mmol/L compared to the simvastatin group (95% CI, 0.48 to 0.90; *P*<0.0001). Significantly greater proportion of patients in the combination therapy group reached TC target (<4 mmol/L) compared to simvastatin group (*P*<0.001). Greater reduction in TG was observed in the combination therapy group compared to the simvastatin group (20.4% vs 12.4%; *P*=0.06). There was no difference in the change of HDL level from baseline between the two groups (~6% increase in each group; *P* value not reported). There was no statistically significant difference in treatment emergent adverse events between the combination therapy and simvastatin groups (40% vs 25%; *P*=0.07).
Chenot et al[69] Simvastatin 40 mg daily vs ezetimibe 10 mg daily added to simvastatin 40 mg daily, separate entities vs no lipid-lowering therapy	RCT Patients, average age 61 years, admitted for an AMI (with or without ST-segment elevation) to the coronary unit, with pain that started within 24 hours of admission; patients were excluded if they had a thyroid disorder, inflammatory disease, neoplasia, serious hepatic disease, creatinine level >1.7	N=60 7 days	Primary: Change from baseline in LDL-C at days 2, 4 and 7, and the achievement of LDL-C <70 mg/dL Secondary: Not reported	Primary: Patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline on days 2, 4, and 7 (27%, 41%, and 51%, respectively; *P*<0.001). Patients on the simvastatin monotherapy experienced a statistically significant LDL-C reduction from baseline on days 2, 4, and 7 (15%, 27%, and 25%, respectively; *P*<0.001). There was no statistically significant change from baseline in LDL-C in the no lipid-lowering therapy group (*P*≥0.09). Patients on the ezetimibe/simvastatin combination therapy achieved lower LDL-C levels compared to the simvastatin monotherapy group at day 4 (*P*=0.03) and day 7 (*P*=0.002) of the study.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	mg/dL, creatinine clearance <30 mL/min, CK >3 times the ULN, LDL-C <90 mg/dL, or were receiving potent 3A4 inhibitors			A greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin monotherapy group at day 4 and day 7 (45% vs 5%, and 55% vs 10%, respectively; *P* value not reported). Secondary: Not reported
McKenney et al[70] COMPELL Rosuvastatin 10 mg for the first 4 weeks, titrated up to 20 mg on weeks 5-8, and 40 mg on weeks 9-12 vs atorvastatin 20 mg for the first 8 weeks, titrated up to 40 mg on weeks 9-12 in addition to niacin SR 500 mg for the first 4 weeks, separate entities, titrated up to 1,000 mg on weeks 5-8, and 2,000 mg on weeks 9-12 vs simvastatin 20 mg for the first 8 weeks, titrated up to 40 mg on weeks 9-12 in addition to ezetimibe 10	MC, OL, PG, RCT Adult patients ≥21 years of age with hypercholesterolemia, eligible for treatment based on the NCEP ATP III guidelines, with two consecutive LDL-C levels within 15% of each other and mean TG ≤300 mg/dL; patients were excluded if they had secondary dyslipidemia, known hypersensitivity to the study drugs, major organ system disease, severe hypertension, diabetes, major cardiovascular event within 12 months, severe heart failure, history of myopathy, active gout, life expectancy <2 years, active liver disease,	N=292 12 weeks	Primary: LDL-C level at week 12 Secondary: HDL-C level at week 12, non–HDL-C, TG, Lp(a), apo B, side effects	Primary: Patients randomized to atorvastatin/niacin SR, rosuvastatin/niacin SR, simvastatin/ezetimibe, and rosuvastatin therapies experienced similar reductions in LDL-C from baseline at week 12 of the study (56%, 51%, 57%, 53%, respectively; *P*=0.093). Secondary: Patients randomized to atorvastatin/niacin SR experienced a statistically significant increase in HDL-C from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin groups (22%, 10%, and 7%, respectively; *P*≤0.05). There was no significant difference in the reduction of non–HDL-C from baseline among treatment groups (*P*=0.053). Patients randomized to atorvastatin/niacin SR experienced a statistically significant reduction in TG from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin groups (47%, 33%, and 25%, respectively; *P*≤0.05). Patients randomized to atorvastatin/niacin SR experienced a statistically significant reduction in Lp(a) from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin 20 mg groups (–14%, +7%, and +18%, respectively; *P*≤0.05). Patients randomized to atorvastatin/niacin SR experienced a statistically significant reduction in apo B from baseline at week 12 of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg, separate entities, for 12 weeks vs rosuvastatin 10 mg for the first 8 weeks, titrated up to 20 mg on weeks 9-12, in addition to niacin SR 500 mg, separate entities, for the first 4 weeks, titrated up to 1,000 mg on weeks 5-12	creatinine clearance <30 mL/min, or uric acid >3 times the ULN			the study compared to the rosuvastatin group (43% vs 39%, respectively; *P*≤0.05). Side effects were similar across treatment groups (*P* value not reported). There were no cases of myopathy or hepatotoxicity reported during the study period.
Primary Prevention of Coronary Heart Disease (CHD) Events				
Colhoun et al[71] CARDS Atorvastatin 10 mg daily after a 6-week placebo run-in period vs placebo daily after a 6-week placebo run-in period	DB, MC, RCT Patients between 40 and 75 years of age with type 2 diabetes without a history of CHD, LDL-C level ≤160 mg/dL, TG ≤600 mg/dL and at least one other CHD risk factor; patients were excluded if they had a past history of an MI, angina, coronary vascular surgery, cerebrovascular accident, severe vascular disease, serum creatinine >150 µmol/L, severe renal dysfunction, nephritic syndrome, HbA_{1c}>12%,	N=2,838 3.9 years	Primary: Major cardiovascular events (CHD death, nonfatal MI, including silent MI on annual ECG, fatal or nonfatal stroke, resuscitated cardiac arrest and coronary revascularization procedures) Secondary: All-cause mortality, acute hospital-verified cardiovascular end point (major CVD events, angina, transient ischemic attack, peripheral	Primary: Atorvastatin treatment led to a 37% reduction in the relative risk of the primary end point compared to control (95% CI, 17 to 52; *P*=0.001). Secondary: Atorvastatin treatment led to a 27% reduction in the relative risk of all-cause mortality compared to control (95% CI, 1 to 48; *P*=0.059). Atorvastatin treatment led to a 32% reduction in the relative risk of any cardiovascular end point compared to control (95% CI, 15 to 45; *P*=0.001). Atorvastatin therapy was associated with a significant reduction in stroke compared to control (1.5% vs 2.8%; HR, 0.52; 95% CI, 0.31 to 0.89; *P* value not reported). Atorvastatin therapy was not associated with a significant reduction in coronary revascularization compared to control (HR, 0.69; 95% CI, 0.41 to 1.16; *P* value not reported). Atorvastatin treatment was associated with a 40% reduction in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	or serum creatine kinase levels >3 times the ULN		vascular disease requiring hospitalization or surgery), reduction in coronary revascularization, lipid reduction	LDL-C levels from baseline compared with control (*P*<0.0001). Atorvastatin treatment was associated with a 26% reduction in the TC levels from baseline compared with control (*P*<0.0001). Atorvastatin treatment was associated with a 1% increase in the HDL-C level from baseline compared with control (*P*=0.0002). Atorvastatin treatment was associated with a 36% reduction in non–HDL-C level from baseline compared with control (*P*<0.0001). Atorvastatin treatment was associated with a 19% reduction in the TG level from baseline compared with control (*P*<0.0001). Atorvastatin treatment was associated with a 23% reduction in apo B level from baseline compared with control (*P*<0.0001). The frequency of adverse events was similar in all study groups (*P* value not reported).
Neil et al[72] CARDS Atorvastatin 10 mg daily after a 6-week placebo run-in period vs placebo daily after a 6-week placebo run-in period	DB, MC, RCT Post hoc analysis of CARDS study, evaluating safety and efficacy of atorvastatin in patients ≥65 years of age (see above)	N=2,838 3.9 years	Primary: Major cardiovascular events (acute CHD death, nonfatal MI, including silent MI on annual ECG, fatal or nonfatal stroke, resuscitated cardiac arrest and coronary revascularization procedures) among patients ≥65 and <65 years of age Secondary: All-cause mortality,	Primary: Atorvastatin treatment led to a 38% reduction in the relative risk of the primary end point in patients ≥65 years of age (95% CI, 8 to 58; absolute risk reduction [ARR], 3.9%, *P*=0.017). Consequently, 21 patients would need to be treated for 4 years to prevent one major cardiovascular event. Atorvastatin treatment led to a 37% reduction in the relative risk of the primary end point in patients <65 years of age (95% CI, 7 to 57; ARR, 2.7%; *P*=0.019). Consequently, 33 patients would need to be treated for 4 years to prevent one major cardiovascular event. Secondary: There was no statistically significant effect on all-cause mortality in either the <65 (*P*=0.98) or the ≥65 year old population (*P*=0.245).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			acute hospital-verified cardiovascular end point (major CVD events, angina, transient ischemic attack, peripheral vascular disease requiring hospitalization or surgery) among patients ≥65 and <65 years of age	Compared to placebo, atorvastatin treatment led to a statistically significant reduction in the LDL-C levels among both the younger and the older patients (38% and 41%, respectively; *P*<0.001). Compared to placebo, atorvastatin treatment led to a statistically significant reduction in the TC levels among both the younger and the older patients (26% and 27%, respectively; *P*<0.001). Compared to placebo, atorvastatin treatment led to a statistically significant reduction in the triglyceride level among both the younger and the older patients (*P*<0.001). The frequency of adverse events was similar in all treatment groups (*P* value not reported).
Hitman et al[73] CARDS Atorvastatin 10 mg daily after a 6-week placebo run-in period vs placebo daily after a 6-week placebo run-in period	DB, MC, RCT Subanalysis of CARDS study, evaluating stroke prevention with atorvastatin therapy (see above)	N=2,838 3.9 years	Primary: Fatal or nonfatal stroke, type of stroke, risk factors for stroke Secondary: Not reported	Primary: Atorvastatin therapy was associated with a significant 48% reduction in stroke compared to control (1.5% vs 2.5%; HR, 0.52; 95% CI, 0.31 to 0.89; *P*=0.016). Atorvastatin therapy was associated with a significant 50% reduction in non-hemorrhagic stroke compared to control (1.1% vs 2.2%; HR, 0.50; 95% CI, 0.27 to 0.91; *P*=0.024). Atorvastatin therapy was associated with a significant 42% reduction in stroke or transient ischemic attacks compared to control (2.1% vs 3.6%; HR, 0.58; 95% CI, 0.37 to 0.92; *P*=0.019). Independent risk factors predicting stroke were age (HR, 2.3; *P*<0.001), microalbuminuria (HR, 2.0; *P*=0.007), and glycemic control (HR, 2.7; *P*=0.007). Women were at a lower risk for stroke than men (HR, 0.3; *P*=0.004). Secondary: Not reported
Sever, Dahlöf et al[74]	DB, MC, RCT	N=10,305	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ASCOT-LLA Atorvastatin 10 mg daily, in addition to antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach systolic and diastolic blood pressure goals of <140 mm Hg and 90 mm Hg, respectively) vs placebo, in addition to antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach systolic and diastolic blood pressure goals of <140 mm Hg and 90 mm Hg, respectively)	Patients between 40 and 79 years of age with either untreated or treated hypertension, TC ≤6.5 mmol/L, and not currently taking a statin or a fibrate; patients were also required to have >3 of the following cardio-vascular disease risk factors: left-ventricular hypertrophy, ECG abnormality, diabetes type 2, PAD, previous stroke or transient ischemic attack, age >55 years, microalbuminuria or proteinuria, male sex, smoking, ratio of plasma TC to HDL-C of >6, or family history of CHD; patients were excluded if they had a previous MI, currently treated angina, cerebrovascular event within 3 months, fasting TG >4.5 mmol/L, heart failure, uncontrolled arrhythmias or any clinically important	3.3 years	Combined end point of nonfatal MI, and fatal CHD Secondary: The primary outcome without silent events, all-cause mortality, total cardiovascular mortality, fatal and nonfatal heart failure, fatal and nonfatal stroke, total coronary end points, and total cardiovascular events and procedures	Compared to placebo, atorvastatin 10 mg daily was associated with a 36% reduction in the primary end point (HR, 0.64; 95% CI, 0.50 to 0.83; *P*=0.0005). Secondary: Compared to placebo, atorvastatin 10 mg daily was associated with a 38% reduction in the primary end point, excluding silent MIs (HR, 0.62; 95% CI, 0.47 to 0.81; *P*=0.0005). Atorvastatin 10 mg daily was not associated with a significant reduction in all-cause mortality (*P*=0.1649), cardiovascular mortality (*P*=0.5066), or fatal and nonfatal heart failure (*P*=0.5794) compared with control. Compared to placebo, atorvastatin 10 mg daily was associated with a 27% reduction in the risk for fatal and nonfatal strokes (HR, 0.73; 95% CI, 0.56 to 0.96; *P*=0.0236). Compared to placebo, atorvastatin 10 mg daily was associated with a 29% reduction in the risk for total coronary events (HR, 0.71; 95% CI, 0.59 to 0.86; *P*=0.005). Compared to placebo, atorvastatin 10 mg daily was associated with a 21% reduction in the risk for total cardiovascular events and procedures (HR, 0.79; 95% CI, 0.69 to 0.90; *P*=0.0005).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	hematological or biochemical abnormality			
Sever, Poulter et al[75] ASCOT-LLA Atorvastatin 10 mg daily, in addition to antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach systolic and diastolic blood pressure goals of <140 mm Hg and 90 mm Hg, respectively) vs placebo, in addition to antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach systolic and diastolic blood pressure goals of <140 mm Hg and 90 mm Hg, respectively)	DB, MC, RCT A two-year extension of the ASCOT-LLA trial (see above)	N=10,305 5.5 years	Primary: Combined end point of nonfatal MI, and fatal CHD Secondary: The primary outcome without silent events, all-cause mortality, total cardiovascular mortality, fatal and nonfatal stroke, fatal and nonfatal heart failure, total coronary end points, and total cardiovascular events	Primary: Compared to placebo, atorvastatin 10 mg daily was associated with a 36% reduction in the primary end point (HR, 0.64; 95% CI, 0.53 to 0.78; *P*≤0.0001). Secondary: Compared to placebo, atorvastatin 10 mg daily was associated with a 19% reduction in the risk for total cardiovascular events and procedures (HR, 0.81; 95% CI, 0.73 to 0.89; *P*≤0.0001). Compared to placebo, atorvastatin 10 mg daily was associated with a 27% reduction in the risk for total coronary events (HR, 0.73; 95% CI, 0.63 to 0.85; *P*≤0.0001). Compared to placebo, atorvastatin 10 mg daily was associated with a 37% reduction in the primary end point, excluding silent MIs (HR, 0.63; 95% CI, 0.51 to 0.77; *P*≤0.0001). Compared to placebo, atorvastatin 10 mg daily was associated with a 23% reduction in the risk for fatal and nonfatal strokes (HR, 0.77; 95% CI, 0.63 to 0.95; *P*=0.0127). Compared to placebo, atorvastatin 10 mg daily was associated with a 15% reduction in the risk for all-cause mortality (HR, 0.85; 95% CI, 0.74 to 0.98; *P*=0.0219). Atorvastatin 10 mg daily was not associated with a significant reduction in cardiovascular mortality (*P*=0.1281), or fatal and nonfatal heart failure (*P*=0.9809) compared with control.
Winkler et al[76] Fluvastatin 20 mg, 40 mg, and 80 mg (pooled group)	MA Double-blind,	N=7,043 (30 studies)	Primary: Major adverse cardiovascular events	Primary: Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of any

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	randomized, placebo-controlled trials assessing ≥6 weeks of fluvastatin therapy in dyslipidemic patients with and without metabolic syndrome	≥6 weeks	(MACEs) defined as CVD-related death, nonfatal MI, and cardiac revascularization, LDL-C, HDL-C, TC, TG, non–HDL-C, apo B Secondary: Not reported	MACE compared to placebo (16% vs 22%; HR, 0.728; 95% CI, 0.6 to 0.9; *P*=0.001). The difference in the incidence of MACE between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (*P*=0.083). Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of a cardiovascular death compared to placebo (3% vs 4.9%; HR, 0.62; 95% CI, 0.4 to 0.95; *P*=0.03). The difference in the incidence of cardiovascular death between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (*P*=0.478). Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of a cardiovascular intervention compared to placebo (12% vs 16%; HR, 0.75; 95% CI, 0.59 to 0.93; *P*=0.011). The difference in the incidence of cardiovascular intervention between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (*P*=0.125). Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of a cardiovascular death or nonfatal MI compared to placebo (6.6% vs 9.9%; HR, 0.65; 95% CI, 0.48 to 0.87; *P*=0.005). The difference in the incidence of cardiovascular death or nonfatal MI between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (*P*=0.288). There was no statistically significant difference in the incidence of nonfatal MI, all-cause mortality, or noncardiovascular-related death between pooled fluvastatin- and placebo-treated patients whether or not they had the metabolic syndrome (*P*>0.05). In all patients, pooled fluvastatin was associated with a significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reduction from baseline in LDL-C, TC, TG, non–HDL-C, and apo B compared to placebo (*P*<0.001). Patients with and without the metabolic syndrome taking fluvastatin experienced similar benefits in terms of LDL-C, TC, non–HDL-C, and apo B reduction from baseline (*P* value not reported). Patients with the metabolic syndrome experienced a greater increase in HDL-C and a greater reduction in TG from baseline compared to patients without the metabolic syndrome (*P*<0.01).
Downs et al[77] AFCAPS/TexCAPS Lovastatin 20 to 40 mg once daily vs placebo once daily	DB, MC, PC, RCT Men aged 45 to 73 years and postmenopausal women aged 55 to 73 years on a low-saturated fat, low-cholesterol diet, with TC 180-264 mg/dL, LDL-C 130-190 mg/dL, HDL ≤45 mg/dL for men or ≤ 47 mg/dL for women and TG ≤400 mg/dL; without a prior history of MI, angina, claudication, cerebrovascular accident, or transient ischemic attack; patients with LDL-C between 125-129 mg/dL were included when the ratio of TC to HDL was more than 6	N=6,605 5.2 years	Primary First acute major coronary event, defined as fatal or nonfatal MI, unstable angina, or sudden cardiac death during at least 5 years of follow-up without clinical evidence of atherosclerotic cardiovascular disease Secondary Fatal or nonfatal coronary revascularization procedure, unstable angina, fatal or nonfatal MI, fatal or nonfatal cardiovascular events, fatal or nonfatal coronary	Primary After an average follow-up of 5.2 years, lovastatin-treated patients experienced a 37% lower incidence of the first acute major coronary event than patients receiving placebo (95% CI, 0.50 to 0.79; *P*<0.001). Secondary Lovastatin-treated patients had 33% reduction in revascularization (95% CI, 0.52 to 0.85; *P*=0.001), 32% reduction in unstable angina (95% CI, 0.49 to 0.95; *P*=0.02), 40% reduction in the incidence of fatal or nonfatal MI (95% CI, 0.43 to 0.83; *P*=0.002), 25% reduction in fatal or nonfatal cardiovascular events (95% CI, 0.62 to 0.91; *P*=0.003), 25% reduction in fatal or nonfatal coronary events (95% CI, 0.61 to 0.92; *P*=0.006) compared to placebo. There were too few events to perform survival analysis on cardiovascular mortality and CHD mortality events based on prespecified criteria (1.0% in lovastatin group vs 1.4% in placebo group and 0.6% in lovastatin group vs 0.9% in lovastatin group, respectively). The overall mortality rate and fatal and nonfatal cancer rates were similar in the lovastatin and placebo groups (*P* value not reported). Discontinuation rates due to adverse events were 13.6% in the lovastatin group and 13.8% in the placebo group (*P* value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			events, cardiovascular mortality and CHD mortality, total mortality, fatal and nonfatal cancer, safety and discontinuation rates	reported). Both treatment groups had similar rates of serious adverse events (34.2% in lovastatin group vs 34.1% in placebo group; *P* value not reported).
The Pravastatin Multinational Study Group for Cardiac Risk Patients (PMS-CRP)[78] Pravastatin 20 to 40 daily vs placebo daily	DB, MC, PC, RCT Men and postmenopausal or surgically sterile women (mean of 55 years of age)	N=1,062 26 weeks	Primary: Lipid levels at 13 and 26 weeks and occurrence of cardiovascular events Secondary: Not reported	Primary: At week 13, when compared to placebo, pravastatin treatment was associated with significant reductions in LDL-C (26%), TC (19%), and TG (12%) and significant elevations in HDL-C (7%) (P<0.001). Throughout the 26 weeks, there were no differences in the total incidence of clinical adverse events between the pravastatin and placebo groups. No MIs or cerebral infarctions occurred in the pravastatin group, and a total of 6 MIs and 3 cerebral infarctions occurred in the placebo group (*P* value not reported). Secondary: Not reported
The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group[79] ALLHAT-LLT Pravastatin 40 mg daily vs usual care Vigorous cholesterol-	MC, OL, RCT Patients aged ≥55 years, with stage 1 or stage 2 hypertension, at least 1 additional CHD risk factor, previously enrolled in the ALLHAT study, fasting LDL-C 120-189 mg/dL for patients with no known CHD or 100-129 mg/dL for patients with known CHD,	N=10,355 Mean 4.8 years (maximum 7.8 years)	Primary: All-cause mortality Secondary: Composite of fatal CHD or nonfatal MI, cause-specific mortality, total and site-specific cancers	Primary: All-cause mortality did not differ significantly between treatment groups (RR, 0.99; 95% CI, 0.89 to 1.11; P=0.88). Secondary: Rates of CHD (fatal CHD plus nonfatal MI) and stroke were slightly lower in the pravastatin group compared to the usual care group (RR, 0.91; 95% CI, 0.79 to 1.04; P=0.16). There were 209 total strokes in the pravastatin group and 231 in the usual care group (RR, 0.91; 95% CI, 0.75 to 1.09; P=0.31). Heart failure rates were similar in the pravastatin and usual care groups (RR, 0.99; 95% CI, 0.83 to 1.18; P=0.89).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
lowering therapy in the usual care group was discouraged.	fasting TG <350 mg/dL			The 6-year cancer rates were similar in both groups (RR, 1.03; 95% CI, 0.89 to 1.19; *P*=0.66).
Nakamura et al[80] MEGA Pravastatin 10-20 mg daily in addition to the NCEP step I diet vs NCEP step I diet	OL, PRO, R Men and post-menopausal women aged 40-70 years weighing ≥40 kg, with hypercholesterolemia, without a history of CHD or familial hypercholesterolemia	N=8,214 Mean 5.2 years	Primary: CHD occurrence, sudden cardiac deaths, MIs, coronary revascularization Secondary: CHD and cerebral infarction, all cardiovascular events, strokes, all-cause mortality	Primary: Pravastatin therapy was associated with a reduced incidence of CHD compared to the control (3.3% vs 5%; HR, 0.67; 95% CI, 0.49 to 0.91; *P*=0.01). There was no statistically significant difference between the groups in either the incidence of sudden cardiac deaths or anginal episodes (*P*>0.05). Secondary: Pravastatin therapy was associated with a reduced incidence of MIs compared to the control (0.9% vs 1.6%; HR, 0.52; 95% CI, 0.29 to 0.94; *P*=0.03). Pravastatin therapy was associated with a reduced incidence of coronary revascularizations compared to the control (2% vs 3.2%; HR, 0.60; 95% CI, 0.41 to 0.89; *P*=0.01). Secondary: Pravastatin therapy was associated with a reduced incidence of CHD and cerebral infarctions compared to the control (5% vs 7.1%; HR, 0.70; 95% CI, 0.54 to 0.90; *P*=0.005). Pravastatin therapy was associated with a reduced incidence of all cardiovascular events compared to the control (6.4% vs 8.5%; HR, 0.74; 95% CI, 0.59 to 0.94; *P*=0.01). There was no statistically significant difference between the groups in either all-cause mortality or the incidence of strokes (*P*>0.05).
Shepherd, Cobbe et al[81] WOSCOPS	DB, PC Men 45 to 64 years of	N=6,595 4.9 years	Primary: Occurrence of nonfatal MI or death	Primary: When compared to placebo, pravastatin produced a 31% reduction in the risk of the combined primary end point of definite nonfatal MI and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Pravastatin 40 mg daily vs placebo daily	age (mean of 55 years of age)		from CHD as a first event Secondary: Occurrence of death from CHD and nonfatal MI	death from CHD (95% CI, 17% to 43%; *P*<0.001). The absolute difference in the risk at five years was 2.4%. Secondary: The reduction in the risk of nonfatal MI was significant whether the definite cases of MI were considered alone or in combination with suspected cases (*P*≤0.001). In the analysis of both definite and suspected cases of death from CHD, there was a significant risk reduction of 33% with treatment (95% CI, 1% to 55%; *P*=0.042), but not in the analysis of definite cases alone (*P* value not reported). When the effect of pravastatin treatment on death from all cardiovascular causes was analyzed, a 32% risk reduction was observed (95% CI, 3% to 53%; *P*=0.033). Additionally, pravastatin treatment was associated with a 31% reduction in the frequency of coronary angiography (95% CI, 10% to 47%; *P*=0.007) and a 37% reduction in the frequency of revascularization procedures (95% CI, 11% to 56%; *P*=0.009).
Ford et al[82] WOSCOPS Pravastatin 40 mg daily for 5 years, with follow-up for subsequent 10 years vs placebo daily for 5 years, with follow-up for subsequent 10 years	DB, RCT Extension of the WOSCOPS study. Male patients, 45 to 64 years of age, with hypercholesterolemia without a history of previous MI, two determinations of LDL-C level ≥155 mg/dL, with at least 1 value that was ≥174 mg/dL	N=6,595 15 years of total follow-up	Primary: Mortality from CHD or nonfatal MI, CHD, cardiovascular causes, all-cause mortality Secondary: Not reported	Primary: Pravastatin treatment led to a statistically significant reduction in the risk of death from CHD or nonfatal MI compared to placebo over a 15-year period (11.8% vs 15.5%; HR, 0.73; 95% CI, 0.63 to 0.83; *P*<0.001). Pravastatin treatment led to a statistically significant reduction in the risk of death from all causes compared to placebo over a 15-year period (18.7% vs 20.5%; HR, 0.88; 95% CI, 0.79 to 0.99; *P*=0.03). Pravastatin treatment led to a statistically significant reduction in the risk of death from cardiovascular causes compared to placebo over a 15-year period (7.6% vs 9.0%; HR, 0.81; 95% CI, 0.68 to 0.96;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and 1 value that was ≤232 mg/dL			*P*=0.01). Pravastatin treatment led to a statistically significant reduction in the risk of death from CHD compared to placebo over a 15-year period (5.1% vs 6.3%; HR, 0.78; 95% CI, 0.64 to 0.96; *P*=0.02). Pravastatin treatment was associated with a small increase in the risk of death from stroke compared to placebo over a 15-year period (1.6% vs 1.1%; HR, 1.37; 95% CI, 0.90 to 2.09; *P*=0.14). Secondary: Not reported
Asselbergs et al[83] Pravastatin 40 mg once daily and fosinopril 20 mg once daily vs placebo two matching tablets once daily	DB, PC, RCT Patients aged 28-75 years with persistent microalbuminuria, blood pressure <160/100 mm Hg (not on antihypertensive medications), TC level <8.0 mmol/L, or <5.0 mmol/L in case of previous MI, and no use of lipid-lowering medication	N=864 46±7 months	Primary: Combined incidence of cardiovascular mortality and hospitalization for cardiovascular morbidity (nonfatal or myocardial ischemia, heart failure, peripheral vascular disease and/or cerebrovascular accident) Secondary: Not reported	Primary: Pravastatin therapy was associated with a 13% reduction in the risk of the primary end point compared to placebo (4.8% vs 5.6%; *P*=0.649). The incidence of noncardiovascular mortality was 2.1% in the pravastatin group compared to 1.9% in the placebo group (*P* value not reported). Secondary: Not reported
Heart Protection Study (HPS) Group[84] MRC/BHF Simvastatin 40 mg once	DB, MC, PC, RCT Patients between the ages of 40-80 years, with a history of CHD, PAD, cerebrovascular	N=20,536 (5,963 diabetics and 14,573 patients with occlusive arterial disease	Primary: Incidence of first nonfatal MI or coronary death, fatal or nonfatal stroke, revascularization	Primary: Simvastatin treatment was associated with a 27% reduction in the incidence of first nonfatal MI or coronary death following randomization (95% CI, 21 to 33; *P*<0.0001) compared to placebo. Among diabetic patients, a 27% reduction in the incidence of first

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily vs placebo once daily	disease, diabetes, or treated hypertension (if also male and >65 years), with TC >135 mg/dL; patients were excluded if statins were contraindicated, if they had had an MI, stroke, or hospital admission for angina within the previous 6 months, if they had chronic liver disease or evidence of liver dysfunction, severe renal dysfunction, inflammatory muscle disease or evidence of muscle problems, concurrent treatment with cyclosporine, fibrates, or high-dose niacin, child-bearing potential, severe heart failure, or other conditions that might limit long-term compliance	without diabetes) 5 years	procedures, first occurrence of major coronary events, strokes, and revascularizations Secondary: Not reported	nonfatal MI or coronary death was observed with simvastatin therapy compared with placebo (95% CI, 19 to 34%; *P*<0.0001). Simvastatin treatment was associated with a significant 25% reduction in the incidence of first nonfatal or fatal strokes following randomization (95% CI, 15 to 34; *P*<0.0001) compared to placebo. Simvastatin treatment was associated with a significant 26% reduction in the incidence of fatal strokes following randomization (95% CI, 14 to 36; *P*=0.0002) compared to placebo. Among diabetic patients, a 24% reduction in the incidence of fatal strokes was observed with simvastatin therapy compared to placebo (95% CI, 6 to 39; *P*=0.01). Simvastatin treatment was associated with a 24% proportional reduction in the incidence of first revascularization procedure following randomization compared with placebo (95% CI, 17 to 30; *P*<0.0001). Among diabetic patients, a 17% reduction in the incidence of first revascularization procedure was observed with simvastatin therapy compared to placebo (95% CI, 3 to 30; *P*=0.02). Simvastatin treatment was associated with a 24% reduction in the first occurrence of major coronary events, strokes, and revascularizations compared to placebo (95% CI, 19 to 28; *P*<0.0001). Among diabetic patients, a 22% reduction in the incidence of first occurrence of major coronary events, strokes, and revascularizations was observed with simvastatin therapy compared to placebo (95% CI, 13 to 30; P<0.0001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
HPS Collaborative Group[85] Simvastatin 40 mg once daily vs placebo once daily	DB, MC, RCT Patients between the ages of 40-80 years, with a history of CHD, PAD, cerebrovascular disease, diabetes, or treated hypertension (if also male and ≥65 years), with TC ≥135 mg/dL; patients were excluded if statins were contraindicated, if they had had an MI, stroke, or hospital admission for angina within the previous 6 months, if they had chronic liver disease or evidence of liver dysfunction, severe renal dysfunction, inflammatory muscle disease or evidence of muscle problems, concurrent treatment with cyclosporine, fibrates, or high-dose niacin, child-bearing potential, severe heart failure, or other conditions that might limit long-term compliance	N=20,536 5 years	Primary: The first major coronary event (nonfatal MI or coronary death), and first major vascular event (major coronary event, stroke or revascularization) Secondary: Not reported	Primary: In the overall study sample, simvastatin resulted in a significant 24% reduction in the first occurrence of a major vascular event, compared to placebo (19.8% vs 25.2%; *P*<0.0001). Among patients with baseline PAD, simvastatin resulted in a significant 22% reduction in the first occurrence of a major vascular event, compared to placebo (26.4% vs 32.7%; *P*<0.0001). Among patients without baseline PAD, simvastatin resulted in a significant 25% reduction in the first occurrence of a major vascular event, compared to placebo (16.5% vs 21.5%; *P*<0.0001). The difference in the reduction of the risk of major vascular events with statin therapy between the PAD and non-PAD groups was not statistically significant (*P*=0.05). In the overall study sample, simvastatin resulted in a significant 27% reduction in the first occurrence of a major coronary event, compared to placebo (8.7% vs 11.8%; *P*<0.0001). Among patients with baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of a major coronary event, compared to placebo (10.9% vs 13.8%; *P*<0.0001). Among patients without baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of a major coronary event, compared to placebo (7.7% vs 10.8%; *P*<0.0001). The difference in the reduction of the risk of major coronary events with statin therapy between the PAD and non-PAD groups was not statistically significant (*P*=0.03). In the overall study sample, simvastatin resulted in a significant 25% reduction in the first occurrence of stroke, compared to placebo (4.3%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				vs 5.7%; *P*<0.0001). Among patients with baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of stroke, compared to placebo (5.3% vs 7.2%; *P*<0.0001). Among patients without baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of stroke, compared to placebo (3.8% vs 5%; *P*<0.0001). The difference in the reduction of the risk of stroke with statin therapy between the PAD and non-PAD groups was not statistically significant (*P*=0.07). In the overall study sample, simvastatin resulted in a significant 24% reduction in the first occurrence of revascularization, compared to placebo (9.1% vs 11.7%; *P*<0.0001). Among patients with baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of revascularization, compared to placebo (13.8% vs 17.9%; *P*<0.0001). Among patients without baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of revascularization, compared to placebo (6.9% vs 8.7%; *P*<0.0001). The difference in the reduction of the risk of revascularization with statin therapy between the PAD and non-PAD groups was not statistically significant (*P*=0.07). In the overall study sample, simvastatin resulted in a significant 16% reduction in the risk of first occurrence of a peripheral vascular event, compared to placebo (4.7% vs 5.5%; *P*=0.006). This risk reduction was independent of baseline LDL-C, age, diabetes, or coronary disease (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Baigent et al[86] Statins (pravastatin 40 mg daily, fluvastatin 40-80 mg daily, simvastatin 20-40 mg daily, atorvastatin 10 mg daily, lovastatin 20-80 mg daily) vs placebo	MA Studies were included if the main effect of ≥1 trial interventions was lipid lowering, there was no confounder, and if ≥1,000 participants participated for at least 2 years.	N=90,056 (14 studies) ≥2 years	Primary: All-cause mortality, CHD mortality, non-CHD mortality Secondary: Effect on CHD death and on major coronary events (nonfatal MI or CHD death) in prespecified subgroups, effect on stroke, cancer, and vascular procedures, vascular events	Primary: There was a 12% reduction in all-cause mortality per 1 mmol/L reduction in LDL cholesterol (RR, 0.88, 95% CI, 0.84 to 0.91; *P*<0.0001). Statin therapy was associated with a 19% reduction in CHD mortality compared with control (3.4% vs 4.4%; RR, 0.81, 95% CI, 0.76 to 0.85; *P*<0.0001). Statin therapy was associated with a nonsignificant 17% reduction in non-CHD mortality compared with control (1.2% vs 1.3%; RR, 0.93, 95 % CI, 0.83 to 1.03; *P* value not reported). Secondary: Statin therapy was associated with a 17% reduction in vascular mortality compared with control (4.7% vs 5.7%; RR, 0.83, 95% CI, 0.79 to 0.87; *P*<0.0001). Statin therapy was associated with a 21% reduction in major vascular events (RR, 0.79, 95% CI, 0.77 to 0.81; *P*<0.0001). Statin therapy was associated with a 26% reduction in nonfatal MI (RR, 0.74, 99% CI, 0.70 to 0.79; *P*<0.0001). Statin therapy was associated with a 23% reduction in any major coronary event (RR, 0.77, 95% CI, 0.74 to 0.80; *P*<0.0001). Statin therapy was associated with a 24% reduction in any coronary revascularization (RR, 0.76, 95% CI, 0.73 to 0.80; *P*<0.0001). Statin therapy was associated with a 21% reduction in any stroke (RR, 0.79, 95% CI, 0.77 to 0.81; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Statin therapy was not associated with a significant increase in the incidence of rhabdomyolysis compared to control (*P*=0.4).
Cholesterol Treatment Trialists' Collaborators[87] Statins (pravastatin 40 mg daily, fluvastatin 40-80 mg daily, simvastatin 20-40 mg daily, atorvastatin 10 mg daily, lovastatin 20-80 mg daily) vs placebo	MA, SA Studies were included if the main effect of ≥1 trial interventions was lipid lowering, there was no confounder, and if ≥1,000 participants participated for at least 2 years.	N=90,056 (14 studies) ≥2 years	Primary: All-cause mortality, CHD mortality, non-CHD mortality among diabetes and non-diabetes patients Secondary: Effect on CHD death and on major coronary events (nonfatal MI or CHD death), major vascular events among diabetic and non-diabetic patients	Primary: Among patients with diabetes, there was a 9% reduction in all-cause mortality per each additional mmol/L reduction in LDL cholesterol (RR, 0.91, 99% CI, 0.82 to 1.01; *P*=0.02). Patients without diabetes experienced a 13% reduction in all-cause mortality per each additional mmol/L reduction in LDL cholesterol (RR, 0.87, 99% CI, 0.82 to 0.92; *P*<0.0001). Secondary: Patients with diabetes experienced a 13% reduction in vascular mortality per mmol/L reduction in LDL cholesterol (RR, 0.87, 99% CI, 0.76 to 1.00; *P*=0.008) and no effect on nonvascular mortality (RR, 0.97, 99% CI, 0.82 to 1.16; *P*=0.7). Among patients with diabetes, there was a 21% reduction in major vascular events per mmol/L reduction in LDL cholesterol (RR, 0.79, 99% CI, 0.72 to 0.86; *P*<0.0001). Patients without diabetes experienced a 21% reduction in major vascular events per mmol/L reduction in LDL cholesterol (RR, 0.79, 99% CI, 0.76 to 0.82; *P*<0.0001). Patients with diabetes experienced a 22% reduction in MI or coronary death (RR, 0.78, 99%CI, 0.69 to 0.87; *P*<0.0001), 25% reduction in coronary revascularization (RR, 0.75, 99% CI, 0.64 to 0.88; *P*<0.0001), and 21% reduction in stroke (RR, 0.79, 99% CI, 0.67 to 0.93; *P*=0.0002). After 5 years of treating 1,000 diabetic patients with statin therapy, 42 patients may be prevented from having a major vascular event (95% CI, 30 to 55; *P* value not reported). The benefit was greater among

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients with diabetes and known vascular disease at baseline.
Secondary Prevention of CHD Events				
Pitt et al[88] AVERT Atorvastatin 80 mg daily vs percutaneous coronary transluminal angioplasty	MC, OL, R Patients, mean age 58.5 years, with stable CAD, LDL-C ≥115 mg/dL and TG ≤500 mg/dL, stenosis ≥50% in at least one coronary artery and had been recommended for treatment with percutaneous revascularization, asymptomatic or with Canadian Cardiovascular Society (CCS) class I or II angina, able to complete at least four minutes of a treadmill test or a bicycle exercise test without marked ECG changes indicative of ischemia; patients were excluded if they had left main CAD, triple-vessel disease, unstable angina or MI within the previous two weeks, and an ejection fraction <40%.	N=341 18 months	Primary: Number of ischemic events and/or need for revascularization, angina symptoms, adverse events Secondary: Not reported	Primary: Compared to revascularization procedure, atorvastatin 80 mg daily was associated with a lower incidence of ischemic events (21% vs 13%; *P*=0.048). Compared to revascularization procedure, atorvastatin 80 mg daily resulted in a significantly longer time to the first ischemic event (*P*=0.03). Compared to revascularization procedure, atorvastatin 80 mg/day resulted in a significantly smaller improvement in the CCS classification of angina symptoms (54% vs 41%; *P*=0.009). The adverse events observed in the study were similar in the two treatment groups (*P* value not reported). Secondary: Not reported
Knopp et al[89]	DB, MC, PG, RCT	N=2,410	Primary: Time to occurrence	Primary: There was no statistically significant difference between atorvastatin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ASPEN Atorvastatin 10 mg once daily vs placebo once daily	Adult patients between 40 and 75 years of age with type 2 diabetes, defined by the World Health Organization, for at least 3 years prior to screening, LDL cholesterol ≤140 mg/dL (if they had a history of an MI, or an interventional procedure >3 months before screening) or LDL cholesterol ≤160 mg/dL, triglyceride level ≤600 mg/dL. Patients were excluded if they had type 1 diabetes, MI, interventional procedure, or episode of unstable angina ≤3 months before screening, HbA_{1C} >10%, active liver disease or hepatic dysfunction, severe renal insufficiency or nephritic syndrome, congestive heart failure treated with digoxin, creatine phosphokinase ≥3 times the ULN, blood pressure >160/100 mm Hg,	4 years	of the composite clinical end point including cardiovascular death, nonfatal MI, nonfatal stroke, recanalization, CABG surgery, resuscitated cardiac arrest, worsening or unstable angina requiring hospitalization Secondary: Time to occurrence of cardiovascular death, noncardiovascular death, transient ischemic attack, worsening or unstable angina not requiring hospitalization, worsening or unstable angina requiring hospitalization, surgery for newly diagnosed PAD, and acute ischemic heart failure requiring hospitalization, cholesterol level reduction, side effects	and placebo groups in the time to first primary event (HR, 90; 95% CI, 0.73 to 1.12; *P*=0.034). Less patients in the atorvastatin group experienced primary end points (13.7%) compared to the placebo group (15%) during the study period (*P*=0.034). Secondary: Atorvastatin group experienced a statistically significant decrease from baseline in the mean LDL-C (~29%) compared to the placebo group (1.6%; *P*<0.0001). Among patients without a prior history of an MI or interventional procedure, 10.4% of atorvastatin- and 10.8% of placebo-treated patients experienced a primary end point (HR, 97; 95% CI, 0.74 to 1.18). Among patients with a prior history of an MI or interventional procedure, 26.2% of atorvastatin- and 30.8% of placebo-treated patients experienced a primary end point (HR, 82; 95% CI, 0.59 to 1.15). Relative risk reductions in fatal and nonfatal MI were 27% overall (*P*=0.10), 19% for patients treated for primary protection (*P*=0.41), and 36% for patients treated for secondary protection (*P*=0.11). Adverse events were similar in both treatment groups for the total, primary, and secondary prevention groups (*P* value not reported). Serious adverse events occurred in 37.7% of patients in the atorvastatin groups and 35.4% of patients receiving placebo (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	BMI>35 kg/m^2, alcohol or drug abuse, hypersensitivity to the study drug, placebo run-in compliance rate <80%, current or planned pregnancy, use of excluded medications, or participation in another study within 30 days			
Schwartz et al[90] MIRACL Atorvastatin 80 mg daily within 96 hours of hospital admission with an acute coronary syndrome (ACS) vs placebo daily within 96 hours of hospital admission with an ACS	DB, I, MC, RCT Patients >18 years of age with unstable angina or non-Q-wave AMI, with chest pain or discomfort of at least 15 minutes duration that occurred at rest or with minimal exertion within the 24-hour period preceding hospitalization and representing a change from their usual anginal pattern; patients were excluded if the serum TC level at screening >270 mg/dL or were planned to have coronary revascul-arization, had Q-wave AMI within 4 weeks, CABG surgery within 3	N=3,086 16 weeks	Primary: A composite end point of death, nonfatal AMI, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia with objective evidence requiring hospitalization Secondary: Occurrence of the individual components of the primary end point, nonfatal stroke, new or worsening heart failure requiring hospitalization, worsening angina requiring hospital-ization but without	Primary: Compared to placebo, atorvastatin 80 mg daily resulted in a 16% reduction in the risk of a composite end point of death, nonfatal AMI, resuscitated cardiac arrest, and recurrent symptomatic myocardial ischemia requiring hospitalization (17.4% vs 14.8%; *P*=0.048). Secondary: Compared to placebo, atorvastatin 80 mg daily resulted in a 26% reduction in the risk of a recurrent ischemia requiring hospitalization (RR, 0.74; 95% CI, 0.57 to 0.95; *P*=0.02). Compared to placebo, atorvastatin 80 mg daily resulted in a 50% reduction in the risk of a fatal and nonfatal stroke (RR, 0.50; 95% CI, 0.26 to 0.99; *P*=0.045). There were no significant differences between groups in the incidence of coronary revascularization procedures, worsening heart failure, worsening angina, occurrence of at least 1 secondary end point, or occurrence of at least 1 primary or secondary end point (*P* value not reported). Liver transaminase elevation was more common in the atorvastatin group than in the placebo group (2.5% vs 0.6%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	months, PCI within 6 months, left bundle-branch block or paced ventricular rhythm, severe congestive heart failure, severe anemia, renal failure requiring dialysis, hepatic dysfunction, insulin-dependent diabetes, pregnancy, were lactating or taking concurrent treatment with other lipid-regulating agents or drugs associated with rhabdomyolysis		new objective evidence of ischemia, coronary revascu-larization, time to occurrence of any of the above, and percent change in lipid levels from baseline, safety	
Olsson et al[91] MIRACL Atorvastatin 80 mg daily within 96 hours of hospital admission with an ACS vs placebo daily within 96 hours of hospital admission with an ACS	DB, I, MC, RCT Post hoc analysis of MIRACL study evaluating atorvastatin therapy in patients ≥65 years of age; patients >18 years of age with unstable angina or non-Q-wave AMI, with chest pain or discomfort of at least 15 minutes duration that occurred at rest or with minimal exertion within the 24-hour period preceding hospitalization and representing a change	N=3,086 16 weeks	Primary: A composite end point of death, nonfatal AMI, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia with objective evidence requiring hospitalization among patients ≥65 and <65 years of age Secondary: Occurrence of the individual components of the	Primary: Compared to placebo, atorvastatin treatment led to a 14% reduction in the relative risk of the primary end point in patients ≥65 years of age (HR, 0.86; 95% CI, 0.70 to 1.07; ARR, 2.9%; *P*=0.18). Compared to placebo, atorvastatin treatment led to a 22% reduction in the relative risk of the primary end point in patients <65 years of age (HR, 0.78; 95% CI, 0.56 to 1.06; ARR, 2.5%; *P*=0.11). Secondary: There was no statistically significant difference in any of the secondary end points between the ≥65 and the <65 age groups (*P*>0.05). The frequency of adverse events was similar in all treatment groups (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	from their usual anginal pattern (see above for exclusion criteria)		primary end point, nonfatal stroke, new or worsening heart failure requiring hospitalization, worsening angina requiring hospitalization but without new objective evidence of ischemia, coronary revascularization, time to occurrence of any of the above, and percent change in lipid levels from baseline among patients ≥65 and <65 years of age	
Athyros, Papageorgiou et al[92] GREACE Atorvastatin 10 mg daily titrated up to 80 mg daily vs usual medical care, consisting of lifestyle modification, pharmacotherapy, including lipid-lowering agents	RCT Adult patients with established CHD not at LDL-C goal (<100 mg/dL), according to the NCEP criteria	N=1,600 3 years	Primary: Death, nonfatal MI, unstable angina, congestive heart failure, revascularization (coronary morbidity), and stroke Secondary: Safety	Primary: Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 51% reduction in the risk for CHD recurrent events or death (24.5% vs 12%; *P*<0.0001). Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 43% reduction in all-cause mortality (5% vs 2.9%; *P*=0.0021). Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 47% reduction in the risk of stroke (2.1% vs 1.1%; *P*=0.034). Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 47% reduction in the risk of coronary mortality (4.8% vs 2.5%; *P*=0.0017).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 54% reduction in the risk of coronary morbidity (*P*<0.0001). Atorvastatin 10 mg titrated to 80 mg daily was associated with a reduction in TC by 36%, LDL-C by 46%, TG by 31%, non–HDL-C by 44%, and an increase in HDL-C by 7% (*P* value not reported). Compared to the usual care, a greater proportion of patients randomized to atorvastatin therapy achieved the NCEP LDL-C treatment goals (3% vs 95%, respectively; *P* value not reported). Compared to the usual care, a greater proportion of patients randomized to atorvastatin therapy achieved the NCEP non–HDL-C treatment goals (14% vs 97%, respectively; *P* value not reported). Secondary: Withdrawals due to adverse effects were similar in the atorvastatin and placebo groups (0.75% vs 0.4%; *P* value not reported).
Athyros, Mikhailidis et al[93] GREACE Atorvastatin 10 mg daily titrated up to 80 mg daily vs usual medical care, consisting of lifestyle modification, pharmacotherapy, including lipid-lowering agents, for other risk	SA Post hoc analysis of the GREACE study; adult patients with established CHD not at LDL-C goal (<100 mg/dL), according to the NCEP criteria, stratified by the presence of metabolic syndrome	N=1,600 3 years	Primary: Vascular events, estimated GFR, serum uric acid level Secondary: Not reported	Primary: Compared to the usual care, daily statin therapy was associated with a 43% reduction in LDL-C from baseline (*P*<0.0001). Among patients with metabolic syndrome, statin therapy was associated with a significant 57% reduction in the incidence of vascular events compared with usual therapy (12.1% vs 28%; RR, 0.43; 95% CI, 0.20 to 0.64; *P*<0.0001). Among patients without metabolic syndrome, statin therapy was associated with a significant 41% reduction in the incidence of vascular events compared with usual therapy (RR, 0.59; 95% CI, 0.41 to 0.79; *P*<0.0001). Statin therapy was associated with a significant increase in GFR and a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
factors (ie, diabetes, hypertension)				reduction in serum uric acid level from baseline (*P*<0.05), regardless of metabolic syndrome status. Usual therapy was associated with a significant reduction in GFR and an increase in serum uric acid level from baseline (*P*<0.05), regardless of metabolic syndrome status. Compared to patients without metabolic syndrome, patients with metabolic syndrome experienced a greater increase in GFR with statin therapy (*P*=0.02). Secondary: Not reported
Serruys et al[94] LIPS Fluvastatin 40 mg twice daily vs placebo twice daily	DB, MC, PC, RCT Men and women aged 18 to 80 years with angina or silent ischemia following successful completion of their first PCI, with baseline TC levels between 135 and 270 mg/dL, with fasting TG <400 mg/dL	N=1,677 3-4 years	Primary: Development of major adverse cardiac events (MACE), defined as cardiac death, nonfatal MI or a reintervention procedure of CABG or repeat PCI Secondary: MACE excluding reintervention procedures (surgical or PCI) occurring in the first 6 months of follow-up for lesions treated at the index procedure, cardiac mortality, combined cardiac mortality and MI, and combined	Primary: MACE-free survival time was significantly longer in the fluvastatin group (*P*=0.01) compared to placebo. Significantly less patients in the fluvastatin group had a MACE compared to patients in the placebo group (21.4% vs 26.7%; RR, 0.78; 95% CI, 0.64 to 0.95; *P*=0.01). During the follow-up period, 13 patients in the fluvastatin group (1.5%) compared to 24 patients in the placebo group (2.9%) died from cardiac causes, 30 patients in the fluvastatin group (3.6%) compared to 38 patients in the placebo group (4.6%) had a nonfatal MI and 167 patients in the fluvastatin group (19.8%) compared to193 patients in the placebo group (23.2%) underwent CABG or PCI (*P* value not reported). Secondary: The risk of MACE, excluding reintervention procedures (surgical or PCI), occurring in the first 6 months of follow-up for lesions treated at the index procedure was 33% lower (RR, 0.67; 95% CI, 0.54 to 0.8; *P*<0.001) in the fluvastatin group than in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			all-cause mortality and MI, and treatment effects on measured lipid levels, discontinuation rates, tolerability, and safety	There was no difference in the reduction of cardiac mortality, combined cardiac mortality and MI, and combined all-cause mortality and MI between the two groups (*P*=0.07, *P*=0.07 and *P*=0.08, respectively). At week 6, fluvastatin significantly reduced LDL-C by 27% (95% CI, 25% to 29%) compared with an 11% reduction seen in the placebo group (95% CI, 9% to 13%; *P*<0.001). Triglyceride reductions were greater in the fluvastatin group compared to placebo (22% vs 14%; *P* value not reported). Levels of HDL increased by a median of 22% in both groups (*P* value not reported). Discontinuation rates due to adverse events were 21.2% in the fluvastatin group and 24.0% in the placebo group. Death rates due to noncardiac causes were 2.7% in the fluvastatin group and 3.0% in the placebo group. There were 3 reported cases of elevations in creatine kinase levels of ≥10 times the ULN in the placebo group. There were 10 patients in the fluvastatin group and 3 patients in the placebo group who had elevations of ≥3 times the ULN level in AST or ALT on 2 consecutive occasions. Cancers were reported in 46 patients in the fluvastatin group and 49 in the placebo group.
Liem et al[95] FLORIDA Fluvastatin 80 mg daily vs placebo daily	DB, PC, PG, RCT Patients, mean age 61 years, with an AMI and TC of <6.5 mmol/L, new or markedly increased chest pain lasting >30 minutes, or a new pathological Q wave of ≥0.04 seconds duration, or ≥25% of	N=540 1 year	Primary Presence of either ischemia on ambulatory ECG monitoring at 12 months or the occurrence of a major clinical event during the study Secondary:	Primary At 12 months, fluvastatin treatment did not significantly affect ischemia on ambulatory ECG (*P*=0.67), nor the occurrence of any major clinical event (*P*=0.24) when compared to placebo. Secondary In patients with ischemia at baseline, 29% in the fluvastatin group and 38% in the placebo group were ischemic on the ambulatory ECG at 6 weeks and 27% in the fluvastatin group and 21% in the placebo group were again positive for ischemia at 12 months (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	the corresponding R wave amplitude, both in at least two contiguous leads		6-week and 12-month occurrence of ischemia on the ambulatory ECG, the 6-week and 12-month change in ischemic burden, the 12-month change in lipid profile, safety and tolerability	The 6-week and 12-month ischemic burden was lowered by 6.1% and 7.7%, respectively in the fluvastatin group and by 10.5% and 13%, respectively in the placebo group (*P*=0.81 and *P*=0.43, respectively between treatment groups) After 12 months, treatment with fluvastatin lowered LDL-C by 21% compared to a 9% increase in the placebo group (*P*<0.001). There were 62 patients in the fluvastatin group and 68 patients in the placebo group who had at least one major clinical event (*P*=0.764). All-cause mortality was 2.6% in the fluvastatin group vs 4% in the placebo group (*P* value not reported).
Sacks et al[96] CARE Pravastatin 40 mg once daily vs placebo once daily	DB, MC, RCT Post MI patients, mean age 59 years, (including men and postmenopausal women), with plasma TC levels <240 mg/dL, LDL-C between 115-174 mg/dL, triglyceride <350 mg/dL, glucose levels ≤220 mg/dL, left ventricular ejection fractions ≥25 percent, and no symptomatic congestive heart failure	N=4,159 5 years	Primary: Death from CHD (including fatal MI, either definite or probable, sudden death, death during a coronary intervention and death from other coronary causes) or a symptomatic nonfatal MI confirmed by serum creatine kinase Secondary: Not reported	Primary: When compared with the placebo group, a 24% lower incidence of the primary end point was observed in the pravastatin group (13.2% vs 10.2%; 95% CI, 9% to 36%; *P*=0.003). Pravastatin therapy was associated with a 23% risk reduction in nonfatal MIs compared with placebo (*P*=0.02). The pravastatin group experienced a nonsignificant 37% reduction in the rate of fatal MIs (95% CI, –5 to 62; *P*=0.07) and a 25% reduction in the rate of total MIs (95% CI, 8 to 39; *P*=0.06) compared with placebo. Secondary: Not reported
The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study	DB, MC, PC Men and women 31 to 75 years of age, who	N=9,014 6.1 years	Primary: Death from CHD Secondary:	Primary: The incidence of the primary study end point of death from CHD was 6.4% in the pravastatin group, as compared with 8.3% in the placebo group (relative reduction in risk, 24%; 95% CI, 12% to 35%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Group[97] Pravastatin 40 mg once daily vs placebo once daily	were post MI or had a hospital discharge diagnosis of unstable angina between 3 and 36 months before study entry		Incidence of MI, stroke, rate of CABG surgery	*P*<0.001). Secondary: Pravastatin therapy was associated with a significant 29% reduction in the incidence of MI compared with placebo (7.4% vs 10.3%; *P*<0.001). Pravastatin therapy was associated with a significant 19% reduction in the incidence of stroke compared with placebo (3.7% vs 4.5%; *P*=0.048). Pravastatin therapy was associated with a significant 22% reduction in the risk of CABG surgery compared with placebo (9.2% vs 11.6%; *P*<0.001). Pravastatin therapy was associated with a significant 19% reduction in the risk of coronary angioplasty compared with placebo (4.7% vs 5.6%; *P*=0.024). Pravastatin therapy was associated with a significant 12% reduction in the risk of unstable angina compared with placebo (22.3% vs 24.6%; *P*=0.005).
Shepherd, Blauw et al[98] PROSPER Pravastatin 40 mg once daily vs placebo once daily	DB, MC, PC, RCT Men and women aged 70-82 years with pre-existing vascular disease (coronary, cerebral, or peripheral) or at an increased risk of such disease due to risk factors (smoking, hypertension, or diabetes), with plasma TC 4.0-9.0 mmol/L, TG <6.0 mmol/L	N=5,804 Mean 3.2 years (range 2.8 to 4.0 years)	Primary: Combined end point of definite or suspect death from CHD, nonfatal MI, and fatal or nonfatal stroke Secondary: Examination of coronary and cerebrovascular components separately, assessment of	Primary: Pravastatin therapy was associated with a significant 15% reduction in the risk of the primary end point compared to placebo (14.1% vs 16.2%; HR, 0.85; 95% CI, 0.74 to 0.97; *P*=0.014). Secondary: When the primary end point was separated into coronary and cerebrovascular components, the authors noted a 19% reduction in coronary events with pravastatin therapy, but no apparent effect on cerebrovascular events (*P* value not reported). Pravastatin therapy was associated with a significant 19% reduction in the risk of CHD death or nonfatal MI compared to placebo (10.1% vs 12.2%; HR, 0.81; 95% CI, 0.69 to 0.94, *P*=0.006).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			cognitive function, adverse events, cancer	When examining the rates of fatal or nonfatal stroke, there was no significant difference between pravastatin and placebo (HR, 1.03; 95% CI, 0.81 to 1.31, *P*=0.81). There was no significant difference in cognitive function between the pravastatin and the placebo groups (*P*>0.05). The rate of serious adverse events reported was similar between both pravastatin and placebo groups (56% vs 55%, respectively; *P* value not reported). There were no participants in either group with rhabdomyolysis or CK concentrations greater than 10 times the ULN (*P* value not reported). There were no significant differences in the rates of cancer development between groups (*P*>0.05).
Thompson et al[99] PACT Pravastatin 20-40 mg daily vs placebo daily	DB, MC, PC, RCT Patients aged 18-85 years with <24 hours onset of symptoms and diagnosis of AMI or unstable angina pectoris	N=3,408 4 weeks	Primary: Composite of death from any cause, AMI, or readmission to hospital with unstable angina pectoris during the first month following randomization Secondary: Incidence of individual causes of death, AMI other than the index event, readmission for angina in the first month, urgent or unscheduled	Primary: Pravastatin 40 mg was associated with a nonsignificant 6.4% reduction in the risk of the primary end point compared with placebo (*P*=0.48). Secondary: There were no significant differences in the frequency of individual components of the primary end point in the 30 days after random assignment among patients assigned to pravastatin compared to placebo (*P*>0.05). The frequency of adverse events did not differ between the study groups (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			revascularization procedure, other nonfatal cardiovascular events, adverse events	
Scandinavian Simvastatin Survival Study (4S) Group[100] Simvastatin 10 mg daily titrated up to 40 mg daily vs placebo daily	DB, PC, RCT Men and women, 35 to 70 years of age, with CHD, a history of angina pectoris or previous MI, and TC 212-309 mg/dL and triglyceride level <221 mg/dL on a lipid-lowering diet	N=4,444 5.4 years	Primary: All-cause mortality Secondary: Major coronary events (coronary deaths, definite or probable hospital-verified nonfatal AMI, resuscitated cardiac arrest, and definite silent MI)	Primary: Simvastatin therapy was associated with a 30% reduction in all-cause mortality compared with placebo (8% vs 12%; RR, 0.70; 95% CI, 0.58 to 0.85; *P*=0.0003). Secondary: Overall, more patients in the placebo group experienced at least one secondary event compared to the simvastatin group (28% vs 19%, respectively; *P* value not reported). There were 189 (8.5%) coronary deaths in the placebo group compared with 111 (5.0%) coronary deaths in the simvastatin group (RR, 0.58; 95% CI, 0.46 to 0.73; *P* value not reported). Definite AMI occurred in 270 (12.1%) patients in the placebo group compared with 164 (7.4%) patients in the simvastatin group. Definite or probable AMI occurred in 418 (18.8%) patients in the placebo group compared with 279 (12.6%) patients in the simvastatin group. Silent MI occurred in 110 (4.9%) patients in the placebo group compared with 88 (4.0%) patients in the simvastatin group. Resuscitated cardiac arrest occurred in 1 patient who was in the simvastatin group. Additionally, a cerebrovascular event occurred in 95 (4.3%) patients in the placebo group compared with 61 (2.7%) patients in the simvastatin group. (RR, 95% CI, and *P* values were not reported for these end points.)
Chonchol et al[101] Scandinavian Simvastatin Survival Study (4S) Simvastatin 10 mg daily	SA Men and women, 35 to 70 years of age, with CHD, a history of angina pectoris or	N=4,444 (4,420 included in the subanalysis) 5.4 years	Primary: All-cause mortality Secondary: Major coronary events (coronary	Primary: Simvastatin therapy was associated with a significant reduction in all-cause mortality among patients with chronic renal insufficiency (HR, 0.70; 95% CI, 0.55 to 0.91; *P* value not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
titrated up to 40 mg daily vs placebo daily	previous MI, and TC 212-309 mg/dL and triglyceride level <221 mg/dL on a lipid-lowering diet, stratified by estimated GFR of ≥75 mL/min/1.73 m^2 or <75 mL/min/1.73 m^2		deaths, definite or probable hospital-verified nonfatal AMI, resuscitated cardiac arrest, and definite silent MI)	Simvastatin therapy was associated with a significant reduction in the incidence of major coronary events among patients with chronic renal insufficiency (HR, 0.68; 95% CI, 0.57 to 0.80; *P* value not reported). Simvastatin therapy was associated with a significant reduction in the incidence of CHD deaths or nonfatal MIs among patients with chronic renal insufficiency (HR, 0.66; 95% CI, 0.55 to 0.79; *P* value not reported). Simvastatin therapy was associated with a significant reduction in the incidence of coronary revascularization among patients with chronic renal insufficiency (HR, 0.63; 95% CI, 0.51 to 0.79; *P* value not reported). Simvastatin therapy was not associated with a significant reduction in the incidence of strokes among patients with chronic renal insufficiency (HR, 0.86; 95% CI, 0.54 to 1.36; *P* value not reported). There were no statistically significant differences in any of the outcome measures between patients with or without chronic renal insufficiency (*P*>0.44).
de Lemos et al[102] A to Z trial Simvastatin 40 mg daily for 1 month, titrated up to 80 mg daily vs placebo daily for 4 months, then simvastatin 20 mg	DB, MC, PC Patients with either non–ST-elevation ACS or ST-elevation MI; median of 61 years of age	N=4,497 2 years	Primary: Composite of cardiovascular death, nonfatal MI, readmission for ACS (requiring new ECG changes or cardiac marker elevation), and stroke Secondary: Individual	Primary: Simvastatin 80-mg therapy was associated with a significant reduction in the risk of the primary end point compared to simvastatin 20-mg therapy (14.4% vs 16.7%; HR, 0.89; 95% CI, 0.76 to 1.04; *P*=0.14). Secondary: Simvastatin 80-mg therapy was associated with a significant reduction in the risk of cardiovascular death compared to simvastatin 20-mg therapy (HR, 0.75; 95% CI, 0.57 to 1.00; *P*=0.05). There was no significant difference observed between treatment groups in the secondary end points of MI, readmission for ACS,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily			components of the primary end point, revascularization due to documented ischemia, all-cause mortality, new-onset congestive heart failure (requiring admission or initiation of heart failure medications), and cardiovascular rehospitalization	revascularization due to documented ischemia, or stroke (*P*>0.05). Simvastatin 80-mg therapy was associated with a significant reduction in the risk of new onset congestive heart failure compared to simvastatin 20-mg therapy (3.7% vs 5.0%; HR, 0.72; 95% CI, 0.53 to 0.98; *P*=0.04).
Briel et al[103] Statins (pravastatin 10-40 mg, fluvastatin 80 mg, atorvastatin 20-80 mg, simvastatin 40-80 mg) vs placebo	MA Randomized, placebo-controlled trials in patients with ACS (MI or unstable angina), started on statin therapy within 14 days of ACS, and with a follow-up ≥30 days; studies were excluded if they compared 2 different statins or included patients with a history of heart transplantation	N=13,024 (12 studies) ≥30 days	Primary: Composite end point of nonfatal MI, nonfatal stroke, and total death Secondary: Total death, total MI, total stroke, cardiovascular death, fatal/nonfatal MI, revascularization procedures (CABG surgery, angioplasty), and unstable angina (recurrent myocardial ischemia requiring emergency hospitalization)	Primary: At either Month 1 or Month 4 of follow-up, there was no statistically significant difference in the primary end point between patients randomized to early statin therapy or placebo (*P*=0.39 and *P*=0.30, respectively). Secondary: At either Month 1 or Month 4 of follow-up, there was no statistically significant difference in any of the secondary end points (except for unstable angina) between patients randomized to early statin therapy or placebo (*P* value not reported). At 4 months of therapy, patients in the early statin group experienced moderate reduction in the incidence of unstable angina compared to the placebo group (*P*=0.05).
Mood et al[104] Statins (atorvastatin 20-40	MA Randomized controlled	N=3,941 (6 studies)	Primary: Incidence of an MI	Primary: Compared to placebo, statin therapy was associated with a 43% reduction in the risk for MI (5.2% vs 3.0%; OR, 0.57; 95% CI, 0.42 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg daily, pravastatin 40 mg daily, fluvastatin 40 mg twice daily) vs placebo	studies comparing statin therapy to placebo or usual care, initiated around the time of a PCI; studies evaluating patients right after an AMI or unstable angina were excluded	up to 45 months	Secondary: All-cause mortality, cardiovascular mortality, surgical or percutaneous revascularization, or stroke	0.78; *P*<0.0001). Secondary: Compared to placebo, statin therapy was associated with a 26% reduction in all-cause mortality (3% vs 2.3%; OR, 0.74; 95% CI, 0.50 to 1.1; *P*=0.14). Compared to placebo, statin therapy was associated with a 42% reduction in cardiovascular mortality (1.2% vs 0.71%; OR, 0.58; 95% CI, 0.30 to 1.11; *P*=0.10). Compared to placebo, statin therapy was associated with an 11% reduction in the incidence of repeat surgical or percutaneous revascularization (21.9% vs 19.6%; OR, 0.89; 95% CI, 0.78 to 1.02; *P*=0.098). The incidence of stroke was higher in the statin group compared to the placebo arm (0.4% vs 0.08%; OR, 3.00; 95% CI, 0.60 to 14.77; *P*=0.18).
Afilalo, Duque et al[105] Moderate statin therapy (pravastatin 40 mg daily, fluvastatin 80 mg daily, simvastatin 20-40 mg daily) vs placebo	MA Randomized controlled trials with at least 6 months of follow-up evaluating ≥50 elderly patients with CHD randomized to a statin or placebo	N=19,569 (9 studies) ≥6 months	Primary: All-cause mortality, CHD mortality, stroke, revascularization, nonfatal MI Secondary: Not reported	Primary: Statin therapy was associated with a lower rate of all-cause mortality compared with placebo (15.6% vs 18.7%; RR, 0.78; 95% CI, 0.65 to 0.89; *P* value not reported). Statin therapy was associated with a reduction in the risk of CHD mortality by 30% (RR, 0.70; 95% CI, 0.53 to 0.83), nonfatal MI by 26% (RR, 0.74; 95% CI, 0.60 to 0.89), revascularization by 30% (RR, 0.70; 95% CI, 0.53 to 0.83), and stroke by 25% (RR, 0.75; 95% CI, 0.56 to 0.94). The calculated number needed to treat with statin therapy to save 1 life was 28 (95% CI, 15 to 56). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bushnell et al[106] Statins vs no statins	MA Patients with CHD or vascular disease	N=22,943 90 days	Primary: Incidence of stroke at 90 days, stroke severity, mortality from strokes, differences between sexes Secondary: Not reported	Primary: Patients reporting the use of statin therapy had lower rates of stroke at 90 days of follow-up (HR, 0.72; 95% CI, 0.53-0.97; *P* value not reported). Statin use was not associated with a significant reduction in stroke mortality (*P*=0.8). Women had an increased risk of experiencing a severe stroke compared with men (*P*=0.035). Statin use was not associated with a significant reduction in stroke severity among women (*P*=0.096). Secondary: Not reported
O'Regan et al[107] Statins (atorvastatin 10-80 mg, simvastatin 20-40 mg, fluvastatin 40-80 mg, pravastatin 10-40 mg, lovastatin 20-73 mg) vs placebo	MA Randomized trials evaluating the effect of statin therapy on all-cause mortality, all-stroke incidence, fatal strokes, hemorrhagic, or ischemic strokes; studies were excluded if reported only surrogate outcomes (eg, LDL-C, HDL-C levels)	N=121,285 (41 primary prevention studies, 1 secondary prevention study) Up to 6 years	Primary All-cause mortality, all-stroke incidence Secondary Incidence of cardiovascular deaths, nonhemorrhagic cerebrovascular events, hemorrhagic strokes, fatal strokes	Primary Compared to placebo, statin therapy was associated with a statistically significant reduction in the risk of all-cause mortality (RR, 0.88; 95% CI, 0.83 to 0.93; *P* value not reported). Compared to placebo, statin therapy was associated with a statistically significant reduction in the risk of strokes (RR, 0.84; 95% CI, 0.79 to 0.91; *P* value not reported). Secondary: Compared to placebo, statin therapy was associated with a statistically significant reduction in the risk of cardiovascular death (RR, 0.81; 95% CI, 0.74 to 0.90; *P* value not reported). Compared to placebo, statin therapy was associated with a statistically significant reduction in the risk of nonhemorrhagic cerebrovascular events (RR, 0.81; 95% CI, 0.69 to 0.94; *P* value not reported). Compared to placebo, statin therapy was associated with a statistically

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				nonsignificant reduction in the risk hemorrhagic strokes (RR, 0.94; 95% CI, 0.68 to 1.30; *P* value not reported). Compared to placebo, statin therapy was associated with a statistically nonsignificant reduction in the risk of fatal strokes (RR, 0.99; 95% CI, 0.80 to 1.21; *P* value not reported). A meta-regression analysis determined that every unit increase in LDL was associated with a 0.3% increased risk of mortality (RR, 1.003; 95% CI, 0.1.0005 to 1.006; *P*=0.02).
LaRosa, Grundy, Waters et al[108] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT Patients between 35-75 years of age, with CHD (either previous MI, coronary revascu-larization, angina with objective evidence of coronary disease); patients were excluded if they had hypersensitivity to statin drugs, current liver disease, nephritic syndrome, pregnancy, uncontrolled CHD risk factors (diabetes, hypertension, etc.), CHD event or revascu-larization within a month, congestive heart failure, unexplained creatine kinase elevation >6 times the ULN, life-threatening	N=10,001 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) Secondary: Individual components of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event, side effects	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 22% reduction in the incidence of primary end point (10.9% vs 8.7%; HR, 0.78; 95% CI, 0.69 to 0.89; *P*=0.0002). Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of strokes (3.1% vs 2.3%; HR, 0.75; 95% CI, 0.59 to 0.96; *P*=0.021). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of cerebrovascular events (5% vs 3.9%; HR, 0.77; 95% CI, 0.64 to 0.93; *P*=0.007). Each 1 mg/dl reduction in LDL-C was associated with a 0.6% relative risk reduction in cerebrovascular events (*P*=0.002) and a 0.5% relative risk reduction in stroke (*P*=0.041). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of nonfatal MIs (6.2% vs 4.9%; HR, 0.78; 95% CI, 0.66 to 0.93; *P*=0.004). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	malignancy, immunosuppressive or lipid-lowering drug treatment.			group experienced a significant reduction in the incidence of major coronary events (8.3% vs 6.7%; HR, 0.80; 95% CI, 0.69 to 0.92; *P*=0.0019). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any coronary events (26.5% vs 21.6%; HR, 0.79; 95% CI, 0.73 to 0.86; *P*<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any cardiovascular events (33.5% vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; *P*<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of hospitalization for heart failure (33.5% vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; *P*<0.0001). There was no statistically significant difference between groups in the incidence of death from CHD (3.3% vs 2.4%; HR, 0.74; 95% CI, 0.59 to 0.94; *P*=0.01). There was no statistically significant difference between groups in the incidence of resuscitation after cardiac arrest (0.5%; HR, 0.96; 95% CI, 0.56 to 1.67; *P*=0.89). There was no statistically significant difference between groups in the incidence of peripheral artery disease (5.6% vs 5.5%; HR, 0.97; 95% CI, 0.83-1.15; *P*=0.76). There was no statistically significant difference between groups in the incidence of death from any cause (5.6% vs 5.7%; HR, 1.01; 95% CI, 0.85 to 1.19; *P*=0.92).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significantly higher incidence of treatment-related adverse events (5.8% vs 8.1%; *P*<0.001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significantly higher incidence of ALT/AST elevations >3 times the ULN (0.2% vs 1.2%; *P*<0.001).
Waters et al[109] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT Subanalysis of TNT study evaluating effects of high-dose atorvastatin on cerebrovascular events; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) (see above for exclusion criteria)	N=10,001 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of primary end point (10.9% vs 8.7%; HR, 0.78; 95% CI, 0.69 to 0.89; *P*=0.0002). Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of strokes (3.1% vs 2.3%; HR, 0.75; 95% CI, 0.59 to 0.86; *P*=0.021). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of cerebrovascular events (5% vs 3.9%; HR, 0.77; 95% CI, 0.64 to 0.93; *P*=0.007). Each 1 mg/dL reduction in LDL-C was associated with a 0.6% relative risk reduction in cerebrovascular events (*P*=0.002) and a 0.5% relative risk reduction in stroke (*P*=0.041). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of nonfatal MIs (6.2% vs 4.9%; HR, 0.78; 95% CI, 0.66 to 0.93; *P*=0.004). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of major coronary events (8.3% vs 6.7%; HR, 0.80; 95% CI, 0.69 to 0.92; *P*=0.0019).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any coronary events (26.5% vs 21.6%; HR, 0.79; 95% CI, 0.73 to 0.86; *P*<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any cardiovascular events (33.5% vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; *P*<0.0001). There was no statistically significant difference between groups in the incidence of transient ischemic attacks (*P*=0.099). There was no statistically significant difference between groups in the incidence of death from CHD (*P*=0.087). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significantly higher incidence of treatment-related adverse events (5.8% vs 8.1%; *P*<0.001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significantly higher incidence of ALT/AST elevations >3 times the ULN (0.2% vs 1.2%; *P*<0.001).
Deedwania, Barter et al[110] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of the TNT study evaluating effects of high-dose atorvastatin in patients with metabolic syndrome; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization,	N=10,001 (subanalysis: N=5,584) 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with metabolic syndrome Secondary:	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 29% reduction in the incidence of primary end point among patient with metabolic syndrome (13% vs 9.5%; HR, 0.71; 95% CI, 0.61 to 0.84; *P*<0.0001). Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of cerebrovascular events among patients with metabolic syndrome (HR, 0.74; 95% CI, 0.59 to 0.93; *P*=0.011).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	angina with objective evidence of coronary disease) and metabolic syndrome (see above for exclusion criteria)		Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event among patients with metabolic syndrome	Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of major coronary events among patients with metabolic syndrome (HR, 0.72; 95% CI, 0.60 to 0.86; *P*=0.0004). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any coronary events among patients with metabolic syndrome (HR, 0.75; 95% CI, 0.67 to 0.83; *P*<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any cardiovascular events among patients with metabolic syndrome (HR, 0.78; 95% CI, 0.71 to 0.85; *P*<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of hospitalization for congestive heart failure among patients with metabolic syndrome (HR, 0.73; 95% CI, 0.55 to 0.96; *P*=0.027). There was no statistically significant difference between groups in the incidence of all-cause mortality among patients with metabolic syndrome (*P* value not reported).
Shepherd, Barter et al[111] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of TNT study evaluating effects of high-dose atorvastatin in patients with diabetes; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective	N=10,001 (subanalysis: N=1,501) 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with diabetes Secondary:	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 25% reduction in the incidence of primary end point among patients with diabetes (17.9% vs 13.8%; HR, 0.75; 95% CI, 0.58 to 0.97; *P*=0.026). Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the time to any cardiovascular events among patients with diabetes (HR, 0.85; 95% CI, 0.73 to 1.00; *P*=0.044).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	evidence of coronary disease) and diabetes, with LDL-C<130 mg/dL (see above for exclusion criteria)		Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event among patients with diabetes	Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 31% reduction in the incidence of time to the first cerebrovascular event among patients with diabetes (HR, 0.69; 95% CI, 0.48 to 0.98; *P*=0.037). There was no statistically significant difference between groups in the incidence of cerebrovascular events among patients with diabetes (*P*=0.437). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of nonfatal MI among patients with diabetes (HR, 0.79; 95% CI, 0.55 to 1.14; *P*=0.202). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of fatal/nonfatal stroke among patients with diabetes (HR, 0.67; 95% CI, 0.43 to 1.04; *P*=0.075). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of death from CHD among patients with diabetes (HR, 0.74; 95% CI, 0.47 to 1.18; *P*=0.203). There was no statistically significant difference between groups in the incidence of major coronary events among patients with diabetes (*P*=0.922). There was no statistically significant difference between groups in the incidence of any coronary events among patients with diabetes (*P*=0.192). There was no statistically significant difference between groups in the incidence of any cardiovascular events among patients with diabetes (*P*=0.458).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no statistically significant difference between groups in the incidence of major cardiovascular events among patients with diabetes (*P*=0.689). There was no statistically significant difference between groups in the incidence of hospitalization with heart failure among patients with diabetes (*P*=0.277). There was no statistically significant difference between groups in the incidence of all-cause mortality among patients with diabetes (*P*=0.521). There was no statistically significant difference between groups in the incidence of PAD among patients with diabetes (*P*=0.789). There was no statistically significant difference between groups in the incidence of treatment-related adverse effects or persistent elevations in liver enzymes (*P* value not reported).
Wenger et al[112] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of the TNT study evaluating effects of high-dose atorvastatin in patients ≥65 years of age; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130	N=10,001 (subanalysis: N=3,809) 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients ≥65 years of age Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 19% reduction in the incidence of primary end point among patients ≥65 years of age (12.6% vs 10.3%; HR, 0.81; 95% CI, 0.67 to 0.98; *P*=0.032). Consequently, in treating 35 patients with atorvastatin 80 mg versus atorvastatin 10 mg, one cardiovascular event could be prevented over a 5-year period. Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was associated with a significant reduction in the incidence of cerebrovascular events among patients ≥65 years of age (*P*=0.010). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of nonfatal MI among patients ≥65 years of age

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	mg/dL (see above for exclusion criteria)		for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event among patients ≥65 years of age	(HR, 0.79; 95% CI, 0.60-1.03; *P*=0.084). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of fatal/nonfatal stroke among patients ≥65 years of age (HR, 0.79; 95% CI, 0.57-1.09; *P*=0.158). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of death from CHD among patients ≥65 years of age (HR, 0.91; 95% CI, 0.63 to 1.29; *P*=0.59). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of resuscitated cardiac arrests among patients ≥65 years of age (HR, 1.19; 95% CI, 0.49 to 2.87; *P*=0.70). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was associated with a significant reduction in the incidence of any cardiovascular events among patients ≥65 years of age (*P*<0.001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was associated with a significant reduction in the incidence of any coronary events among patients ≥65 years of age (*P*<0.001). Compared to atorvastatin 10 mg group, atorvastatin 80 mg group was associated with a significant reduction in incidence of hospitalization for heart failure among patients ≥65 years of age (*P*=0.008). There was no statistically significant difference between groups in the incidence of major coronary events among patients ≥65 years of age (*P*=0.128). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				of death from cardiovascular causes among patients ≥65 years of age (HR, 0.91; 95% CI, 0.67 to 1.24; *P*=0.55). Compared to the atorvastatin 10 mg group, more patients in the atorvastatin 80 mg group died from noncardiovascular causes among patients ≥65 years of age (HR, 1.26; 95% CI, 0.93 to 1.70; *P*=0.129). More patients ≥65 years of age randomized to the atorvastatin 80 mg group experienced treatment-related adverse events compared to the atorvastatin 10 mg group (*P* value not reported).
Khush et al[113] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of TNT study evaluating effects of high-dose atorvastatin on hospitalization for heart failure; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130 mg/dL (see above for exclusion criteria)	N=10,001 5 years	Primary: Hospitalization for heart failure among patients with and without a history of heart failure Secondary: Not reported	Primary: Prior history of heart failure is a significant risk factor for hospitalization from heart failure. While 14.1% of patients with heart failure at baseline were hospitalized for heart failure, only 1.9% of patients who did not have heart failure at baseline were hospitalized for heart failure during the study period (*P*<0.001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was associated with a significant reduction in the incidence of hospitalization from heart failure among patients with heart failure at baseline (17.3% vs 10.6%; HR, 0.59; 95% CI, 0.4 to 0.80; *P*=0.008). Mortality was significantly higher among patients with heart failure compared to patients without heart failure at baseline (15% vs 4.9%; *P*<0.001). Each reduction of 1 mg/dL in LDL-C was associated with a reduction in the risk of hospitalization for heart failure by 0.6% (*P*=0.007). Secondary: Not reported
LaRosa, Grundy, Kastelein et al[114] TNT	DB, MC, PG, RCT, SA Post hoc analysis of TNT study evaluating	N=10,001 (subanalysis: N=9,769)	Primary: First major cardiovascular event (death from CHD,	Primary: Patients in the lowest quintiles were associated with the most reduction in the primary end point (*P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	effects of VLDL-C levels achieved with atorvastatin on cardiovascular end points and mortality; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130 mg/dL (see above for exclusion criteria)	5 years	nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with LDL-C <64 mg/dL (Quintile 1), 64 to ≤77 mg/dL (Quintile 2), 77 to ≤90 mg/dL (Quintile 3), 90 to ≤106 mg/dL (Quintile 4), and ≥106 mg/dL (Quintile 5) Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event among patients classified as Quintile 1, 2, 3, 4, or 5 (from above)	Secondary: Patients in the lowest quintiles were associated with the most reduction in the risk of death from CHD (*P*<0.01). Patients in the lowest quintiles were associated with the most reduction in the risk of nonfatal MIs (*P*<0.0001). Patients in the lowest quintiles were associated with the most reduction in the risk of stroke (*P*<0.05). There were no significant differences in the incidence of all-cause mortality across quintiles (*P*=0.104). There were no significant differences in the incidence of cardiovascular mortality across quintiles (*P*=0.060). There were no significant differences in the incidence of all-cause mortality across quintiles (*P*=0.653). There were no significant differences in the incidence of treatment-related adverse effects across quintiles (*P* value not reported).
Barter et al[115] TNT Atorvastatin 10 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of TNT study evaluating effects of HDL-C levels	N=10,001 (subanalysis: N=9,770) 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI,	Primary: Patients in the highest HDL-C quintiles were associated with the greatest reduction in the primary end point (*P*=0.04). Compared to patients in Quintile 1, patients classified as Quintile 5 had

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs atorvastatin 80 mg daily	achieved with atorvastatin on cardiovascular end points; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130 mg/dL (see above for exclusion criteria		resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with HDL-C <38 mg/dL (Quintile 1), 38 to 42 mg/dL (Quintile 2), 43 to 47 mg/dL (Quintile 3), 48 to 54 mg/dL (Quintile 4), and ≥55 mg/dL (Quintile 5) Secondary: Not reported	a 25% reduction in risk of a major cardiovascular event (HR, 0.75; 95% CI, 0.60 to 0.95). An increase in 1 mg/dL in the HDL-C reduces the risk of major cardiovascular events by 1.1% at 3 months (*P*=0.003). Patients with the lowest ratio of LDL-C to HDL-C were at a lower risk for major cardiovascular events (*P*=0.006). Patients with the lowest ratio of TC to HDL-C were at a lower risk for major cardiovascular events (*P* value not reported). Among patients whose LDL-C was <70 mg/dL, those in the highest HDL-C quintile were at the lowest risk for a major cardiovascular event (*P*=0.03). Secondary: Not reported
Shepherd, Kastelein et al[116] TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Subanalysis of TNT study evaluating nephroprotective effects of atorvastatin; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130 mg/dL (see above for exclusion criteria)	N=10,001 (subanalysis: N=9,770) 5 years	Primary: GFR Secondary: Not reported	Primary: Patients randomized to atorvastatin 80 mg daily experienced a significant increase in GFR from baseline over a 5-year study period compared with the atorvastatin 10 mg daily group (*P*<0.0001). Secondary: Not reported
Pedersen et al[117]	MC, OL, PG, RCT	N=8,888	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IDEAL Atorvastatin 80 mg daily vs simvastatin 20 mg daily	Patients ≤80 years of age with a history of an MI and qualifying for statin therapy based on NCEP ATP III guidelines; patients were excluded if they had liver enzyme elevation >2 times the ULN, pregnancy or breastfeeding, nephrotic syndrome, uncontrolled diabetes, uncontrolled hypothyroidism, plasma triglyceride levels >600 mg/dL, congestive heart failure, valvular heart disease, malabsorption condition, treatment with other drugs interfering with statin therapy, and treatment with other lipid-lowering drugs	~4.8 years	Occurrence of a major coronary event (coronary death, confirmed nonfatal AMI, or cardiac arrest with resuscitation) Secondary: Major cardiovascular events (any primary event and stroke), any CHD event (any primary event, any coronary revascularization procedure, or hospitalization for unstable angina), any cardiovascular events	Atorvastatin therapy was associated with a nonsignificant reduction in the risk of a major coronary events compared with simvastatin therapy (9.3% vs 10.4%; HR, 0.89; *P*=0.07). Secondary: Atorvastatin therapy was associated with a significant reduction in the risk of a nonfatal MI compared with simvastatin therapy (6% vs 7.2%; HR, 83; *P*=0.02). Atorvastatin therapy was associated with a significant reduction in the risk of major cardiovascular events compared with simvastatin therapy (12% vs 13.7%; HR, 87; *P*=0.02). Atorvastatin therapy was associated with a significant reduction in the risk of any cardiovascular events compared with simvastatin therapy (26.5% vs 30.8%; HR, 84; *P*<0.001). Atorvastatin therapy was associated with a significant reduction in the risk of any CHD event compared with simvastatin therapy (20.2% vs 23.8%; HR, 84; *P*<0.001). Atorvastatin therapy was associated with a significant reduction in the risk of peripheral vascular disease compared with simvastatin therapy (2.9% vs 3.8%; HR, 76; *P*=0.02). Atorvastatin therapy was associated with a nonsignificant reduction in the risk of death from noncardiovascular cause compared with simvastatin therapy (3.2% vs 3.5%; HR, 92; *P*=0.47). Atorvastatin therapy was associated with a nonsignificant reduction in the risk fatal/nonfatal stroke compared with simvastatin therapy (3.4% vs 3.9%; HR, 87; *P*=0.20). Atorvastatin therapy was associated with a nonsignificant reduction in the risk hospitalization for nonfatal heart failure compared with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				simvastatin therapy (2.2% vs 2.8%; HR, 81; *P*=0.11). Atorvastatin therapy was associated with a nonsignificant reduction in the risk of all-cause mortality compared with simvastatin therapy (8.2% vs 8.4%; HR, 98; *P*=0.81). Atorvastatin therapy was associated with a higher rate of drug discontinuations due to adverse effects compared with simvastatin therapy (9.6% vs 4.2%; *P*<0.001). Atorvastatin therapy was associated with a higher rate of liver transaminase elevations compared with simvastatin therapy (*P*<0.001). There was no significant difference between treatment groups in the incidence of serious adverse events (*P*=0.42).
Cannon, Braunwald et al[118] PROVE IT–TIMI 22 Atorvastatin 80mg daily vs pravastatin 40mg daily	DB, DD, MC, RCT Men and women ≥18 years of age (mean age 58.9 years), in stable condition after a hospitalization for an ACS with either an AMI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to six months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-	N=4,162 Up to 3 years (mean 2 years)	Primary Rates of composite death from any cause, MI, documented unstable angina requiring hospitalization, revascularization, and stroke Secondary Risk of death due to CHD, nonfatal MI, or revascularization and the risk of the individual components of the primary end points, discontinuation rates, tolerability and side	Primary The rates of composite death from any cause, MI, unstable angina requiring hospitalization, revascularization, and stroke at two years were 26.3% in the pravastatin group and 22.4% in the atorvastatin group, representing a 16% reduction in the hazard ratio favoring atorvastatin (95% CI, 5% to 26%; *P*=0.005). Secondary The risk of death due to CHD, nonfatal MI, or revascularization was reduced by 14% in the atorvastatin group (*P*=0.029) with a two-year event rate of 19.7% compared with 22.3% in the pravastatin group. The risk of death, MI, or urgent revascularization was reduced by 25% in the atorvastatin group (*P*<0.001). Among the individual components of the primary end point, atorvastatin-treated patients had significant reduction of 14% for revascularization (*P*=0.04) and a 29% reduction in the risk of recurrent unstable angina (*P*=0.02) compared to the pravastatin group. There were nonsignificant reductions in the rates of death or MI (18%, *P*=0.06) and the rates of stroke (*P* value not reported) between the two

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL		effects	groups. The discontinuation rates due to adverse events or for other reasons were 21.4% in the pravastatin group and 22.8% in the atorvastatin group at one year (*P*=0.30) and 33% and 30.4%, respectively at two years (*P*=0.11). Discontinuation rates due to myalgias or muscle aches or elevation in creatine kinase levels were 2.7% in the pravastatin group and 3.3% in the atorvastatin group (*P*=0.23). There were 1.1% of patients in the pravastatin group and 3.3% in the atorvastatin group who had elevations in ALT levels that were ≥3 times the ULN (*P*<0.001).
Ray, Cannon et al[119] PROVE IT-TIMI 22 Atorvastatin 80 mg daily (intensive regimen) vs pravastatin 40 mg daily (standard regimen)	DB, RCT Subanalysis of PROVE IT-TIMI 22 study evaluating the timing of effects with statin therapy; patients, mean age 58.9 years, with an ACS within 10 days of randomization, stable for at least 24 hours (see above for exclusion criteria)	N=4,162 up to 3 years (mean 2 years)	Primary: A composite of all-cause mortality, MI, unstable angina requiring hospitalization, revascularization, or stroke Secondary: A composite of death, MI, or unstable angina requiring hospitalization	Primary: At 30 days, 3% of intensive regimen group experienced a primary end point compared with 4.2% in the standard treatment group (HR, 72; 95% CI, 0.52 to 0.99; *P*=0.046). From 6 months to the end of the study, 15.1% of intensive regimen group experienced a primary end point compared with 17.7% in the standard treatment group (HR, 82; 95% CI, 0.69 to 0.99; *P*=0.037). Secondary: Atorvastatin therapy was associated with a significant reduction in the risk of the triple composite end point compared with pravastatin therapy (15.7% vs 20%; HR, 76; 95% CI, 0.66 to 0.88; *P*=0.0002). At 30 days, patients randomized to the intensive statin regimen experienced a greater reduction in LDL-C and CRP level from baseline compared to the standard statin regimen group (*P*<0.001).
Ahmed et al[120] PROVE IT-TIMI 22 Atorvastatin 80 mg daily (intensive regimen)	RCT, SA Subanalysis of PROVE IT-TIMI 22 study evaluating effects of atorvastatin in patients with diabetes; patients,	N=4,162 Up to 3 years (mean 2 years)	Primary: A composite of death, MI, unstable angina requiring hospitalization, revascularization with PCI, or CABG	Primary: There was no statistically significant difference between the pravastatin and atorvastatin groups in terms of the primary end point among patients with diabetes (31.8% vs 28.4%; HR, 88; *P*=0.28). Secondary: Intensive atorvastatin therapy resulted in a significantly lower event

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs pravastatin 40 mg daily (standard regimen)	mean age 58.9 years, with an ACS within 10 days of randomization, stable for at least 24 hours (see above for exclusion criteria)		surgery occurring within 30 days after randomization, or stroke within 2 years after study onset Secondary: A composite of death, MI, or unstable angina requiring hospitalization, LDL-C <70 mg/dL goal, hsCRP <2 mg/L goal, MI, unstable angina requiring hospitalization	rate for the secondary composite end point compared with the standard pravastatin regimen among patients with diabetes (21.1% vs 26.6%; HR, 0.75; *P*=0.03) and patients without diabetes (14% vs 18%; HR, 0.76; *P*=0.002). Consequently, treating 1,000 diabetic and nondiabetic patients with intensive statin regimen would prevent 55 and 40 events, respectively (*P* value not reported). Compared with nondiabetic patients, fewer patients with diabetes on the intensive statin regimen achieved the dual goal of LDL-C <70 mg/dL and hsCRP <2 mg/L (37.6% vs 45.4%; *P*=0.004). Out of diabetic patients treated with intensive statin therapy, 62% failed to reach the dual goal of LDL-C <70 mg/dL and hsCRP <2 mg/L. Diabetic patients who reached the dual LDL-C/CRP goal had significantly lower rates of the secondary end point compared to patients who failed to reach the goal (17.7% vs 24.7%; *P*=0.021). In the diabetic population, among the individual components of the primary and secondary composite end points, the only variable exhibiting a statistically significant reduction with intensive statin therapy compared with the standard regimen was unstable angina requiring hospitalization (3.1% vs 7.4%; *P*=0.003).
Scirica et al[121] PROVE IT-TIMI 22 Atorvastatin 80 mg daily (intensive regimen) vs	DB, DD, RCT Subanalysis of PROVE IT-TIMI 22 study evaluating effects of atorvastatin on hospitalization for heart failure; patients, mean age 58.9 years, with an	N=4,162 up to 3 years (mean 2 years)	Primary: Hospitalization for heart failure occurring at least 30 days after randomization Secondary: Not reported	Primary: Patients randomized to the intensive statin group experienced a statistically significant reduction in the rate of hospitalization for heart failure compared to the control group (1.6% vs 3.1%; HR, 0.55; 95% CI, 0.35 to 0.85; *P*=0.008). The benefit observed with the intensive statin therapy was independent on recurrent MI or prior history of heart failure. Higher B-type natriuretic peptide (BNP) was associated with an

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pravastatin 40 mg daily (standard regimen)	ACS within 10 days of randomization, stable for at least 24 hours, with TC <240 mg/dL (see above for exclusion criteria)			increased risk for heart failure (HR, 2.6; 95% CI, 1.2 to 5.5; *P*=0.016). Among patients with a high BNP level (>80 pg/mL), intensive statin therapy was associated with a lower incidence of heart failure compared to patients randomized to the standard statin regimen (HR, 0.32; 95% CI, 0.13 to 0.8; *P*=0.014). Secondary: Not reported
Ray, Bach et al[122] Atorvastatin 80 mg daily (intensive regimen) vs pravastatin 40 mg daily (standard regimen)	RCT, SA Subanalysis of PROVE IT-TIMI 22 study evaluating effects of atorvastatin in patients ≥70 years of age. Patients, mean age 58.9 years, with an ACS within 10 days of randomization, stable for at least 24 hours; patients were excluded if they had uncontrolled diabetes (fasting plasma glucose ≥230 mg/dL, an episode of hyperosmolar non-ketotic coma or ketoacidosis) within 6 months of study onset, stratified by age <70 and ≥70 years	N=4,162 up to 3 years (mean 2 years)	Primary: Cardiac mortality, MI, unstable angina requiring hospitalization, relationship between NCEP goal and a composite primary end point of all-cause mortality, MI, unstable angina requiring hospitalization, revascularization, or stroke Secondary: A composite of death, MI, or unstable angina requiring hospitalization	Primary: At 30 days, a greater proportion of patients in both age groups randomized to atorvastatin therapy achieved the NCEP goals compared with pravastatin therapy (*P*<0.001). Among the elderly, the achievement of the NCEP LDL-C goal was associated with an 8% reduction in the risk of primary end point from baseline (*P*=0.008). The younger age group achieving the NCEP LDL-C goal was associated with a 2.3% reduction in the risk of primary end point from baseline (*P*=0.013). Younger patients were associated with a lower risk of the primary composite end point compared to the older age group (23% vs 30.4%; *P* <0.0001). Younger patients were associated with a lower risk of all-cause mortality (*P*<0.0001), MIs (*P*<0.0001), unstable angina requiring hospitalization (*P*=0.01), or strokes (*P*=0.004) compared to the older age group. Secondary: The composite triple end point occurred more frequently in the elderly compared to the younger age group (20.1% vs 11%; HR, 1.93; 95% CI, 1.59 to 2.33; *P*<0.0001).
Deedwania, Stone et al[123]	DB, DD, MC, PG, RCT	N=893	Primary: Absolute change in	Primary: At 12 months, the total duration of ischemia was significantly reduced

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
SAGE Atorvastatin 80 mg daily (intensive regimen) vs pravastatin 40 mg daily (standard regimen)	Ambulatory CAD patients, between 65 and 85 years of age, with ≥1 episode of myocardial ischemia that lasted ≥3 minutes during a 48-hour ambulatory ECG at screening, and baseline LDL-C level between 100 mg/dL and 250 mg/dL; patients were excluded if they had atrial fibrillation or heart failure, NYHA stage III or IV	12 months	the total duration of myocardial ischemia on 48-hour Holter monitor from baseline to month 12 Secondary: Absolute change in the total duration of myocardial ischemia on 48-hour Holter monitor from baseline to month 3, the percent change in the total duration of myocardial ischemia from baseline to months 3 and 12, the absolute and percent change in the number of ischemic episodes from baseline to months 3 and 12, the percent change in ischemic burden, the proportion of patients free of ischemia at months 3 and 12, the percent change in the levels of TC, LDL-C, HDL, TG, and apo B	from baseline in both groups (*P*<0.001). There was no statistically significant difference between the pravastatin and atorvastatin groups in terms of the primary end point (*P*=0.88). Secondary: There were no statistically significant differences between the pravastatin and atorvastatin groups in any of the secondary end points assessing degree of ischemia at month 3 or 12 (*P* value not reported). Atorvastatin therapy was associated with a 77% reduction in all-cause mortality relative to pravastatin therapy over a 12-months period (HR, 0.33; 95% CI, 0.13 to 0.83; *P*=0.014). Compared with pravastatin, therapy with atorvastatin was associated with a significantly greater reductions in TC, LDL-C, TG, and apo B at months 3 and 12 (*P*<0.001). Compared with atorvastatin, therapy with pravastatin was associated with a significantly greater increase in the level of HDL cholesterol at months 3 (*P*<0.001) and 12 (*P*=0.009). Atorvastatin therapy was associated with a higher incidence of liver test abnormalities compared to pravastatin therapy (17.3% vs 13.9%; *P*<0.001). There were no statistically significant differences between the pravastatin and atorvastatin groups in treatment related adverse events (13.9% vs 17.3%; *P*=0.17).
Sakamoto et al[20] MUSASHI-AMI	I, MC, RCT Patients, mean age 63.5 years, randomized to	N=486 ~416 days	Primary: A composite end point of ACS events, such as	Primary: Hydrophilic statin therapy was associated with a lower incidence of ACS events compared to the lipophilic statin therapy (3.6% vs 9.9%; *P*=0.053).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lipophilic statins* (atorvastatin 9.3 mg, fluvastatin 26.8 mg, pitavastatin 2 mg, simvastatin 5 mg) within 96 hours of hospital admission with an AMI vs hydrophilic statin* (pravastatin 9.4 mg) within 96 hours of hospital admission with an AMI Pitavastatin is not commercially available in the Unites States. * Doses represent the mean daily doses evaluated in the study.	statin or no statin therapy within 96 hours of an AMI, with TC between 190 and 240 mg/dL		cardiovascular death, nonfatal MI, recurrent acute myocardial ischemia requiring emergency hospitalization Secondary: Occurrence of the individual components of the primary end point, nonfatal stroke, heart failure requiring emergent rehospitalization, new Q-wave appearance on the ECG	Secondary: Hydrophilic statin therapy was associated with a lower incidence of new Q-wave appearance on the ECG compared to the lipophilic statin therapy (75% vs 89%; *P*=0.0056). There was no statistically significant difference in any of the other secondary end points between the two groups (*P*=0.339).
Hulten et al[124] Intensive statin therapy (pravastatin 40 mg daily, fluvastatin 80 mg daily, simvastatin 80 mg daily, atorvastatin 20 mg daily, atorvastatin 80 mg daily) vs placebo or lower-dosed statin therapy	MA Randomized controlled trials in adults started on intensive statin therapy or control within 14 days of hospitalization for ACS	N=17,963 (13 studies) Up to 2 years of follow-up	Primary: Composite end point of death, recurrent ischemia, and recurrent MI, death and cardiovascular events, cardiovascular death, ischemia, MI, LDL-C reduction, side effects Secondary: Not reported	Primary: In patients with recent ACS, intensive statin therapy was associated with lower mortality and cardiovascular events over 24 months of follow-up (HR, 0.81; 95% CI, 0.77 to 0.87; *P*<0.001). In patients with recent ACS, intensive statin therapy was associated with a lower risk of overall cardiovascular events over 24 months of follow-up (HR, 0.84; 95% CI, 0.76 to 0.94; *P* value not reported). In patients with recent ACS, intensive statin therapy was associated with lower cardiovascular mortality over 24 months of follow-up (HR, 0.76; 95% CI, 0.66 to 0.87).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In patients with recent ACS, intensive statin therapy was associated with lower ischemia over 24 months of follow-up (HR, 0.68; 95% CI, 0.50 to 0.92). In patients with recent ACS, intensive statin therapy was not associated with a lower incidence of MIs over 24 months of follow-up (HR, 0.89; 95% CI, 0.60 to 1.33). Intensive statin therapy was associated with a greater reduction in LDL-C compared with controls (*P*<0.001). Adverse effects were similar with the intensive statin therapy and the controls (*P* value not reported). Secondary: Not reported
Afilalo, Majdan et al[125] Moderate statin therapy (pravastatin ≤40 mg daily, lovastatin ≤40 mg daily, fluvastatin ≤40 mg daily, simvastatin ≤20 mg daily, atorvastatin ≤10 mg daily, rosuvastatin ≤5 mg daily) vs intensive statin therapy (simvastatin 80 mg daily, atorvastatin 80 mg daily, rosuvastatin 20-40 mg daily)	MA Randomized controlled trials with at least 6 months of follow-up evaluating patients with recent ACS or stable CHD randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=28,505 (6 studies) ≥6 months	Primary: All-cause mortality, CHD mortality, hospitalization for heart failure, major coronary event (cardiovascular death or ACS), stroke, adverse effects Secondary: Not reported	Primary: In patients with recent ACS, intensive statin therapy was associated with lower all-cause mortality (OR, 0.75; 95% CI, 0.61 to 0.93). By treating 90 people with intensive statin therapy, one death could be prevented. All-cause mortality was not reduced by intensive statin therapy among patients with stable CHD (OR, 0.99; 95% CI, 0.89 to 1.11). In patients with recent ACS, intensive statin therapy was associated with a reduction in the incidence of major coronary events (OR, 0.86; 95% CI, 0.73 to 1.01). In patients with stable CHD, intensive statin therapy was associated with a reduction in the incidence of major coronary events (OR, 0.82; 95% CI, 0.75 to 0.91). Treating 46 patients with intensive statin therapy may prevent one major coronary event.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In patients with recent ACS, intensive statin therapy was associated with a reduction in the incidence of heart failure hospitalizations (OR, 0.63; 95% CI, 0.46 to 0.86). In patients with stable CHD, intensive statin therapy was associated with a reduction in the incidence of heart failure hospitalizations (OR, 0.77; 95% CI, 0.64-0.92). Treating 112 patients with intensive statin therapy may prevent one hospitalization for heart failure. Intensive statin therapy was associated with a threefold increase in adverse hepatic (OR, 3.73; 95% CI, 2.11 to 6.58) and muscular events (OR, 1.96; 95% CI, 0.50 to 7.63). Consequently, 96 people would need to be treated, for one patient to experience an adverse hepatic event. Secondary: Not reported
Cannon, Steinberg et al[126] Intensive statin therapy (simvastatin 40-80 mg daily, atorvastatin 80 mg daily) vs moderate statin therapy (pravastatin 40 mg daily, simvastatin 20 mg daily, atorvastatin 10 mg daily)	MA Randomized controlled trials evaluating patients with recent ACS or stable CHD randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=27,548 (4 studies) Up to 5 years	Primary: Combined incidence of coronary death or nonfatal MI, the combined incidence of coronary death or any cardiovascular event (MI, stroke, hospitalization for unstable angina, or revascularization), incidence of stroke, incidence of cardiovascular, non-cardiovascular, and all-cause mortality	Primary: Intensive statin therapy was associated with an overall significant odds reduction of 16% for coronary death or MI compared to moderate statin therapy (9.4% vs 8.0%; OR, 0.84; 95% CI, 0.77 to 0.91; *P*<0.00001). Intensive statin therapy was associated with an overall significant odds reduction of 16% for coronary death or any cardiovascular event compared to moderate statin therapy (32.3% vs 28.8%; OR, 0.84; 95% CI, 0.80 to 0.89; *P*<0.0000001). Intensive statin therapy was associated with a reduction in cardiovascular mortality of 12% compared to moderate statin therapy (3.8% vs 3.3%; OR, 0.88; 95% CI, 0.78 to 0.1.00; *P*=0.054). Intensive statin therapy was not associated with lower non-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	cardiovascular mortality compared to the moderate statin therapy (*P*=0.73). Intensive statin therapy was not associated with statistically significant reduction in all-cause mortality compared to the moderate statin therapy (6.2% vs 5.9%; *P*=0.20). Intensive statin therapy was associated with an overall significant odds reduction of 18% for stroke compared to moderate statin therapy (2.8% vs 2.3%; OR, 0.82; 95% CI, 0.71 to 0.96; *P*=0.012). Intensive statin therapy was associated with an overall significant odds reduction of 16.5% for CHD death or MI compared to moderate statin therapy (OR, 0.835; 95% CI, 0.77 to 0.91; *P*<0.0001). Secondary: Not reported
Murphy et al[127] A to Z PROVE-IT–TIMI 22 Intensive statin therapy (simvastatin 40-80 mg daily, atorvastatin 80 mg daily) vs moderate statin therapy (pravastatin 40 mg daily, simvastatin 20 mg daily)	MA Randomized controlled trials evaluating patients with recent ACS, clinically stable for 12-24 hours, randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=8,658 (2 studies) Up to 2 years	Primary: Incidence of cardiovascular, non-cardiovascular, and all-cause mortality Secondary: Not reported	Primary: Intensive statin therapy was associated with a significant 23% reduction in the risk of all-cause mortality, compared to moderate statin therapy (3.6% vs 4.9%; HR, 0.77; 95% CI, 0.63 to 0.95; *P*=0.015). Intensive statin therapy was associated with a significant 24% reduction in the risk of cardiovascular mortality, compared to moderate statin therapy (2.6% vs 3.5%; HR, 0.76; 95% CI, 0.59 to 0.97; *P*=0.025). Intensive statin therapy was not associated with a significant reduction in the risk of noncardiovascular mortality, compared to moderate statin therapy (1% vs 1.4%; HR, 0.82; 95% CI, 0.55 to 1.21; *P*=0.32). Secondary: Not reported
Adverse Effects				

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Silva, Swanson et al[128] Statins (atorvastatin, pravastatin, simvastatin, lovastatin, fluvastatin, rosuvastatin) vs placebo	MA Randomized, prospective studies comparing statin therapy with placebo with a follow-up >6 weeks, reporting data on nonfatal adverse events	N=71,108 (18 studies) up to 317 weeks	Primary: Adverse events, cardiovascular events Secondary: Not reported	Primary: Statin therapy increased the risk of any adverse events by 39% compared with placebo (OR, 1.4; 95% CI, 1.09 to 1.80; *P*=0.008). Consequently, out of 197 patients treated with statin therapy, one patient would experience an adverse event (95% CI, 24 to 37; *P* value not reported). Statin therapy was associated with a 26% reduction in the risk of a clinical cardiovascular event compared with placebo (OR, 0.74; 95% CI, 0.69 to 0.80; *P*<0.001). Consequently, the number needed-to-treat to prevent 1 additional cardiovascular event was 27. Rosuvastatin studies were not included in the analysis of cardiovascular risk reduction due to inadequate data. The incidence of adverse effects during statin administration was observed in the following order, from highest to lowest: atorvastatin >pravastatin= simvastatin= lovastatin> fluvastatin. Secondary: Not reported
Kashani et al[129] Statins (atorvastatin 20-80 mg, fluvastatin 2.5-80 mg, lovastatin 10-80 mg, pravastatin 10-160 mg, rosuvastatin 1-80 mg, simvastatin 2.5-80 mg) vs placebo	MA Randomized, double-blinded studies comparing statin therapy with placebo in adult patients (≥18 years of age) with hyperlipidemia, reporting data on adverse events; all studies were required to randomly allocate ≥100 patients to statin monotherapy vs	N=74,102 (35 studies) up to 65 months	Primary: Adverse events (myalgia, CK elevation, rhabdomyolysis, transaminase elevation), discontinuation due to adverse event; results expressed in terms of the risk difference (RD) per 100 patients Secondary:	Primary: Statin therapy was not associated with a statistically significant increase in the risk of myalgias (RD, 2.7; 95% CI, –3.2 to 8.7; *P*=0.37), CK elevation (RD, 0.2; 95% CI, –0.6 to 0.9; *P*=0.64), rhabdomyolysis (RD, 0.4; 95% CI, –0.1 to 0.9; *P*=0.13), or discontinuation due to adverse events (RD, –0.5; 95% CI, –4.3 to 3.3; *P*=0.80) compared with placebo. Statin therapy was associated with a statistically significant risk of transaminase elevations (RD, 4.2; 95% CI, 1.5 to 6.9; *P*<0.01) compared with placebo. When individual statins were compared to placebo, atorvastatin was the only statin with a statistically significant increase in the risk of myalgias (*P*=0.04).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	placebo		Not reported	When individual statins were compared to placebo, fluvastatin (*P*<0.01) and lovastatin (*P*=0.05) were the only statins with a statistically significant increase in the risk of transaminase elevation. Secondary: Not reported
McClure et al[130] Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin), stratified by ≤40 mg and >40 mg daily lovastatin equivalent dose vs placebo	MA Randomized, controlled, double-blind studies comparing statin therapy with placebo in adult patients (≥18 years of age) with hyperlipidemia, reporting data on adverse events	N=86,000 (119 studies) Up to 65 months	Primary: Adverse events (myalgia, myositis, rhabdomyolysis), discontinuations due to adverse events; results expressed in terms of Peto odds ratios (POR), in order to account for rare or zero events Secondary: Not reported	Primary: Statin therapy was not associated with a statistically significant increase in the risk of myalgias (POR, 1.09; 95% CI, 0.97 to 1.23; *P*=0.471), rhabdomyolysis (POR, 1.59; 95% CI, 0.54 to 4.70; *P*=0.544), or myositis (POR, 2.56; 95% CI, 1.12 to 5.85; *P*=0.987) compared with placebo. Statin therapy was associated with a lower incidence of discontinuations due to adverse events (POR, 0.88; 95% CI, 0.84 to 0.93; *P*<0.001) compared with placebo. Secondary: Not reported
Newman et al[131] Atorvastatin 10 mg once daily vs atorvastatin 80 mg once daily vs placebo once daily	MA Studies evaluating adverse effects of atorvastatin administered to patients with various cardiovascular risks, LDL-C level ≥130 mg/dL and triglyceride level ≤600 mg/dL	N=14,236 (42 studies) Between 2 weeks and 52 months	Primary: Adverse effects Secondary: Not reported	Primary: Treatment-related side effects were similar across all study groups (*P* value not reported). Treatment-associated myalgia was observed in 1.4%, 1.5%, and 0.7% of patients receiving atorvastatin 10 mg, 80 mg, and placebo, respectively (*P* value not reported). No cases of rhabdomyolysis were reported among the study groups (*P* value not reported). Elevations in hepatic transaminases >3 times the ULN were observed in 0.1%, 0.6%, and 0.2% of patients receiving atorvastatin 10 mg, 80 mg, and placebo, respectively (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Shepherd, Hunninghake et al[132] Rosuvastatin 5-40 mg once daily vs atorvastatin 10-80 mg once daily vs simvastatin 10-80 mg once daily vs pravastatin 10-40 mg once daily vs placebo once daily	MA Randomized, controlled studies comparing statin therapy with placebo or comparator statins in patients with dyslipidemia; patients with secondary dyslipidemia or with a history of serious hypersensitivity reaction to statin therapy were excluded	N=16,876 (33 studies) 25,670 patient-years	Primary: Adverse events, elevation in transaminases, CK, myopathy, dipstick-positive proteinuria, estimated glomerular rate Secondary: Not reported	Primary: The incidence of adverse events was similar in the rosuvastatin and the placebo groups (52.1% vs 51.8%, respectively; *P* value not reported). The incidence of adverse events was similar across all the active treatment groups (*P* value not reported). The incidence of elevation in transaminases, and CK, myopathy, dipstick-positive proteinuria, and estimated glomerular rate was similar across all the active treatment groups (*P* value not reported). Secondary: Not reported
Dale et al[133] Intensive-dose statin therapy including hydrophilic statins (atorvastatin 80 mg) and lipophilic statins (simvastatin 40-80 mg,	MA Randomized, comparative studies comparing intensive- and moderate-dose statin therapies in at least 100 patients, with	N=21,765 (9 studies) up to 5 years	Primary: Incidence of elevations in AST, ALT or CK Secondary: Not reported	Primary: Intensive statin therapy was associated with an increased risk of AST, or ALT elevation, compared to the moderate-dose statin therapy (1.5% vs 0.4%; RR, 3.10; 95% CI, 1.72 to 5.58; *P*=0.002). Intensive statin therapy was not associated with a statistically significant risk of CK elevation, compared to the moderate-dose statin therapy (0.1% vs 0.02%; RR, 2.63; 95% CI, 0.88 to 7.85; *P*=0.89).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
lovastatin 76 mg) vs moderate-dose statin therapy including hydrophilic statins (atorvastatin 10 mg, pravastatin 40 mg) and lipophilic statins (simvastatin 20-40 mg, lovastatin 4 mg)	a follow-up ≥48 weeks, reporting data on the incidence of elevations in AST, ALT or CK			In a subanalysis of hydrophilic and lipophilic statins, while no cases of CK elevation occurred in the hydrophilic intensive-dose statin group, patients on lipophilic intensive-dose statin therapy experienced a non–statistically significant risk in CK elevation (RR, 6.09; 95% CI, 1.36 to 27.35; *P*≥0.11). Secondary: Not reported
Silva, Matthews et al[134] Intensive-dose statin therapy (atorvastatin 80 mg, simvastatin 80 mg) vs moderate-dose statin therapy (atorvastatin 10 mg, simvastatin 20 mg, pravastatin 40 mg)	MA Randomized, comparative studies comparing intensive- and moderate-dose statin therapies for the reduction of secondary cardiovascular events in patients with ACS or stable CAD	N=27,548 (4 studies) ~3.4 years	Primary: CK ≥10 times the ULN, with or without myalgia, ALT or AST ≥3 times the ULN, rhabdomyolysis, drug-induced adverse effects requiring drug discontinuation, any drug-induced adverse event, all-cause mortality, cardiovascular death, nonfatal MI, and stroke Secondary: Not reported	Primary: Intensive statin therapy was associated with an increased risk of any adverse event compared with the moderate-dose statin therapy (OR, 1.44; 95% CI, 1.33 to 1.55; *P*<0.001). Consequently, out of 30 patients treated with intensive statin therapy, one patient would experience an adverse event (95% CI, 24 to 37; *P* value not reported). Intensive statin therapy was associated with an increased risk (absolute risk, 2.14%) of an adverse drug event requiring discontinuation of drug therapy (OR, 1.28; 95% CI, 1.18 to 1.39; *P*≤0.001). Intensive statin therapy was associated with an increased risk (absolute risk, 1.2%) of an elevation in AST/ALT ≥3 times the ULN (OR, 4.84; 95% CI, 3.27 to 6.16; *P*≤0.001). Consequently, out of 86 patients treated with intensive statin therapy, one patient would experience an elevation in AST/ALT ≥3 times the ULN (95% CI, 72 to 106; *P* value not reported). Intensive statin therapy was associated with an increased risk (absolute risk, 0.07%) of an elevation in CK ≥10 times the ULN (OR, 9.97; 95% CI, 1.28 to 77.92; *P*=0.028). Consequently, out of 1,534 patients treated with intensive statin therapy, one patient would experience an elevation in CK ≥10 times the ULN (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no statistically significant difference in the incidence of rhabdomyolysis between the study groups (*P* value not reported). Intensive statin therapy was not associated with a significant reduction in all-cause mortality compared to the moderate-dose statin therapy (*P*=0.185). Intensive statin therapy was associated with a significant reduction in the risk for cardiovascular death (*P*=0.031), nonfatal MI (*P*<0.001), and stroke (*P*=0.004). Consequently, the number needed-to-treat to prevent 1 additional cardiovascular death, MI, or stroke was 229, 99, and 166, respectively. Secondary: Not reported
Law et al[135] Statins (lovastatin, atorvastatin, pravastatin, simvastatin, fluvastatin); doses were not reported vs placebo	Systematic Review Cohort studies, randomized, placebo-controlled studies, voluntary adverse events notification to national regulatory authorities, and published individual case reports	2 cohort studies and 21 RCTs (N=not reported) Up to 6.1 years	Primary: Incidence of rhabdomyolysis, myopathy, renal failure, elevated ALT, renal failure, proteinuria, peripheral neuropathy Secondary: Not reported	Primary: The incidence of rhabdomyolysis associated with the use of statins in two cohort and randomized, controlled studies was 3.4 (95% CI, 1.6 to 6.5) per 100,000 patient-years (*P* value not reported). The incidence of rhabdomyolysis associated with the use of statins in addition to gemfibrozil in two cohort studies was 35 (95% CI, 1 to 194) per 100,000 patient-years (*P* value not reported). The notification of rhabdomyolysis to the FDA adverse events reporting system was approximately 4 times higher in patients receiving lovastatin, simvastatin, or atorvastatin compared with those on monotherapy with fluvastatin or pravastatin (*P*<0.001). The notification of rhabdomyolysis to the FDA adverse events reporting system was approximately 15 times higher in patients receiving statins in combination with gemfibrozil (21 per 100,000 patient-years; 95% CI, 17 to 25) compared with those on statin monotherapy (0.70 per 100,000 patient-years; 95% CI, 0.62 to 0.79;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P<0.001). The incidence of myopathy associated with the use of statins in randomized, controlled studies was 5 (95% CI, –17 to 27) per 100,000 patient-years (*P* value not reported). The incidence of liver failure associated with the use of statins, reported to the FDA adverse events reporting system, was 0.1 per 100,000 patient-years of use (*P* value not reported). Statin use in patients with elevated ALT would lead to liver disease in <1 person (*P* value not reported). Statin use was not associated with a higher incidence of renal failure or proteinuria than with placebo (*P* value not reported). Patients receiving statin therapy have 1.8 odds of experiencing peripheral neuropathy compared with placebo (95% CI, 1.1 to 3.0; *P*<0.001). Secondary: Not reported

Study abbreviations: ARR=absolute risk reduction, CI=confidence interval, DB=double blind, DD=double dummy, ES=extension study, FU=follow-up, HR=hazard ratio, MA=meta-analysis, MC=multicenter, MN=multinational, I=international, OR=odds ratio, OL=open label, PC=placebo-controlled, PG=parallel group, POR=Peto odds ratio, PRO=prospective trial, R=randomized, RCT=randomized controlled trial, RD=risk difference, RR=risk ratio or relative risk, SB=single blind, SA=subanalysis

Miscellaneous abbreviations: ACS=acute coronary syndrome, ALT=alanine aminotransferase, ALT=alanine transaminase, AMI=acute myocardial infarction, apo AI=apoliprotein AI, apo B=apolipoprotein B, apo E=apoliprotein E, AST=aspartate aminotransferase, BMI=body mass index, BP=blood pressure, CABG=coronary artery bypass graft, CAC=coronary artery calcification, CAD=coronary artery disease, CCS=Canadian Cardiovascular Society, CDP=Coronary Drug Project, CHD=coronary heart disease, CIMT=carotid intima-media thickness, CK=creatine kinase, CPK=creatinine phosphokinase, CRP=C-reactive protein, CV=cardiovascular, CVD=cardiovascular disease, CVD=cerebrovascular disease, ECG=electrocardiogram, FBG=fasting blood glucose, FPG=fasting plasma glucose, FSG=fasting serum glucose, GFR=glomerular filtration rate, HbA_{1c}=hemoglobin A1c, HDL=high-density lipoprotein, HDL-C=high-density lipoprotein cholesterol, hsCRP=high-sensitivity C-reactive protein, IMT= intima-medial thickness, LDL=low-density lipoprotein, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MACE=major adverse cardiac events, MI=myocardial infarction, NCEP=National Cholesterol Education Program, NCEP ATP III=National Cholesterol Education Program, Adult Treatment Panel III, NYHA=New York Heart Association , PAD=peripheral arterial disease, PAV=percent atheroma volume, PCI=percutaneous coronary intervention, TAV=total atheroma volume, TC=total cholesterol, TG=triglycerides, ULN=upper limit of normal, VLDL-C=very low-density lipoprotein, VLDL-TG=very low-density lipoprotein triglycerides

IX. Conclusions

The single entity HMG-CoA reductase inhibitors (statins) are FDA approved for the treatment of primary hypercholesterolemia and mixed dyslipidemia.[1,4-10] Atorvastatin, rosuvastatin, and simvastatin are also FDA approved for the treatment of homozygous familial hyperlipidemia in adjunction with other lipid-lowering treatments. Atorvastatin, lovastatin, pravastatin, and simvastatin are indicated for primary prevention of cardiovascular events in patients at risk but without clinically evident coronary heart disease (CHD). Atorvastatin, fluvastatin, pravastatin and simvastatin are also FDA approved for secondary prevention of cardiovascular events in patients with clinically evident CHD. To date, rosuvastatin has not been approved for the primary and/or secondary prevention of cardiovascular events but has been shown to reduce the rate of change in carotid intima-media thickness and atheroma volume.[1,9,25,26] Rosuvastatin is the only statin without an FDA indication for use in pediatric patients with heterozygous familial hypercholesterolemia. All these agents are formulated for once-daily oral administration, with lovastatin and fluvastatin available as sustained-release tablet formulations. Subsequent to their longer half-life, atorvastatin, rosuvastatin, and sustained-release fluvastatin may be taken at any time of the day, while the other statins should be administered in the evening. Lovastatin, pravastatin, and simvastatin are available generically.

The agents in this class have demonstrated a significant benefit in reducing total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), and modestly increasing high-density lipoprotein cholesterol (HDL-C).[1,2,4-11,27-122] With the exception of rosuvastatin, the statins have been shown to reduce the risk of all-cause mortality, cardiovascular mortality, and cardiovascular morbidity. All of the statins have demonstrated the ability to delay the progression of coronary atherosclerosis among patients with and without established CHD. Furthermore, numerous studies have demonstrated the added benefit of aggressive lipid-lowering with statin therapy in reaching NCEP ATP III LDL-C goals as well as prolonging CHD-free survival.[52-54,101-122]

All statins may cause an elevation in liver enzymes and creatinine kinase, sometimes accompanied by myopathy and rarely rhabdomyolysis and renal failure. Consequently, liver function tests should be performed routinely with statin therapy. However, statins are generally well-tolerated and the common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. There are some differences among the statins with regards to drug interactions. Pravastatin is the only statin with low protein binding, leading to a lower risk of a drug interaction with warfarin. Pravastatin and rosuvastatin do not undergo extensive first-pass metabolism and are therefore associated with a low risk for drug-drug interactions.[1,2,18] Atorvastatin, lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin is metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles as noted in Table 6. I n patients with severe renal impairment, atorvastatin and fluvastatin are the only statins that do not require dosage adjustments.[1,2] All statins are contraindicated in patients with active liver disease.

The NCEP ATP III guidelines and the European Guidelines on Cardiovascular Disease Prevention designate statins as first-line agents for the treatment of patients with hypercholesterolemia, failing therapeutic lifestyle modification, at high risk for cardiovascular events as well as patients suffering from heterozygous familial hypercholesterolemia.[11,12] High-dose statin therapy is also recognized as moderately effective for patients with homozygous familial hypercholesterolemia.[12] The NCEP ATP III guidelines have established criteria for initiating lipid-lowering therapy. According to the criteria, the target LDL-C level <100 mg/dL is a therapeutic goal for patients with established CHD or CHD risk equivalent (ie, diabetes); however, an LDL-C goal of <70 mg/dL may be arbitrarily preferred for these high-risk patients. In addition, LDL-C goals of <130 mg/dL and <160 mg/dL are designated for patients at moderate and low risk for CHD, respectively. While the statins differ in their LDL-lowering potential as noted in Table 2, there are no clinical studies that have demonstrated that one statin is more efficacious than another with regards to clinical outcomes. If LDL-C goal is not reached after 6 weeks of therapy with a statin, either an elevation of dose or the addition of a second lipid-lowering agent is appropriate.[12]

X. Recommendations

In recognition of the well-established role of the HMG-CoA Reductase Inhibitors as primary therapy for cholesterol reduction and reduction in cardiovascular morbidity and mortality; their extended track record of efficacy & safety; and current consensus standards encouraging even lower LDL-C target goals, no changes are recommended to the current approval criteria.

Simvastatin, lovastatin, and pravastatin are preferred on The Office of Vermont Health Access (OVHA) preferred drug list. Crestor® is available without a prior authorization after a generic simvastatin trial (i.e. the patient has had a documented side effect, allergy, or treatment failure to generic simvastatin)..

Zocor®, Lipitor® require prior authorization with the following approval criteria:

- The patient has had a documented side effect, allergy, or treatment failure to both generic simvastatin and Crestor®

Altoprev®, Lescol®, Lescol® XL, Mevacor®, Pravachol®

- The patient has had a documented side effect, allergy, or treatment failure to both generic lovastatin and pravastatin.

References

1. Cardiovascular drugs 24:00, Antilipemic agents 24:06, HMG-CoA reductase inhibitors 24:06.08. In: McEvoy GK, editor; American Hospital Formulary Service. AHFS drug information 2007 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2007 [cited 2008 Jan 30]. Available from: http://online.statref.com.
2. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2007 [cited 2008 Jan 30]. Available from: http://www.thomsonhc.com/.
3. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008 Jan 29;117(4):e25-146.
4. Lipitor® [package insert]. New York (NY): Pfizer Inc; 2007 Nov.
5. Lescol®, Lescol XL® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2006 Oct.
6. Mevacor® [package insert]. Whitehouse Station (NJ): Merck & Co, Inc; 2007 Dec.
7. Altoprev® [package insert]. Atlanta (GA): Sciele Pharma, Inc; 2006 Dec.
8. Pravachol® [package insert]. Princeton (NJ): Bristol-Myers Squibb; 2007 Mar.
9. Crestor® [package insert].Wilmington (DE): AstraZeneca Pharmaceuticals LP; 2007 Nov.
10. Zocor® [package insert]. Whitehouse Station (NJ): Merck & Co, Inc; 2007 May.
11. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004 Jul 13;110(2):227-39. Available from: http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3upd04.htm.
12. National Institutes of Health: National Cholesterol Education Program. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report [guideline on the Internet]. Circulation. 2002 Dec 17 [cited 2007 Dec 26];106(25):3143-421. Available from: http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf.
13. Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, et al; American Heart Association; American College of Cardiology; National Heart, Lung, and Blood Institute. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation. 2006 May 16;113(19):2363-72. Available from: http://www.americanheart.org/presenter.jhtml?identifier=3004572.
14. Institute for Clinical Systems Improvement (ICSI). Healthcare guideline: lipid management in adults [guideline on the Internet]. 10th ed. Bloomington (MN): Institute for Clinical Systems Improvement; 2007 Jun [cited 2007 Dec 19]. Available from: http://www.icsi.org/lipid_management_3/lipid_management_in_adults_4.html.
15. McCrindle BW, Urbina EM, Dennison BA, Jacobson MS, Steinberger J, Rocchini AP, et al; American Heart Association. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. Circulation. 2007 Apr 10;115(14):1948-67. Available from: http://www.americanheart.org/presenter.jhtml?identifier=3004597.
16. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, et al. European guidelines on cardiovascular disease prevention in clinical practice: Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil. 2007 Sep;14 Suppl 2:S1-113. Available from: http://www.escardio.org/knowledge/guidelines/.
17. Drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2008 Jan 30]. Available from: http://www.utdol.com/utd/index.do.
18. Drug Facts and Comparisons 4.0 [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2007 [cited 2008 Jan 30]. Available from: http://online.factsandcomparisons.com.
19. Talbert RL. Hyperlipidemia. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach. 6th ed. New York: McGraw-Hill; 2005; 429-52.
20. Sakamoto T, Kojima S, Ogawa H, Shimomura H, Kimura K, Ogata Y, et al. Usefulness of hydrophilic vs lipophilic statins after acute myocardial infarction: subanalysis of MUSASHI-AMI. Circ J. 2007 Sep;71(9):1348-53.
21. Hamelin BA, Turgeon J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. Trends Pharmacol Sci. 1998 Jan;19(1):26-37.

22. FDA public health advisory for Crestor (rosuvastatin) [press release on the Internet]. Rockville (MD): Food and Drug Administration (US): 2004 Jun 9 [cited 2008 Jan 30]. Available from: http://www.fda.gov/cder/drug/advisory/crestor.htm.
23. Furberg CD, Adams HP, Applegate WB, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic carotid artery progression study (ACAPS) research group. Circulation. 1994; 90(4):1679-87.
24. Byington RP, Furberg CD, Crouse JR, et al. Pravastatin, lipids, and atherosclerosis in the carotid arteries (PLAC-II). Am J Cardiol. 1995; 76:54C-9C.
25. Crouse JR 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA. 2007 Mar 28; 297(12):1344-53.
26. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006 Apr 5;295(13):1556-65.
27. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, et al; ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008 Apr 3;358(14):1431-43. Epub 2008 Mar 30.
28. Yu CM, Zhang Q, Lam L, Lin H, Kong SL, Chan W, et al. Comparison of intensive and low-dose atorvastatin therapy in the reduction of carotid intima-medial thickness in patients with coronary heart disease. Heart. 2007 Aug;93(8):933-9.
29. Schmermund A, Achenbach S, Budde T, Buziashvili Y, Förster A, Friedrich G, et al. Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. Circulation. 2006 Jan 24;113(3):427-37.
30. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA; REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004 Mar 3;291(9):1071-80.
31. Schoenhagen P, Tuzcu EM, Apperson-Hansen C, Wang C, Wolski K, Lin S, et al. Determinants of arterial wall remodeling during lipid-lowering therapy: serial intravascular ultrasound observations from the Reversal of Atherosclerosis with Aggressive Lipid Lowering Therapy (REVERSAL) trial. Circulation. 2006 Jun 20;113(24):2826-34.
32. Nicholls SJ, Tuzcu EM, Sipahi I, Schoenhagen P, Hazen SL, Ntanios F, et al. Effects of obesity on lipid-lowering, anti-inflammatory, and antiatherosclerotic benefits of atorvastatin or pravastatin in patients with coronary artery disease (from the REVERSAL Study). Am J Cardiol. 2006 Jun 1;97(11):1553-7.
33. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J; Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005 Jan 6;352(1):29-38.
34. Rodenburg J, Vissers MN, Wiegman A, van Trotsenburg AS, van der Graaf A, de Groot E, et al. Statin treatment in children with familial hypercholesterolemia: the younger, the better. Circulation. 2007 Aug 7;116(6):664-8.
35. Avis HJ, Vissers MN, Stein EA, Wijburg FA, Trip MD, Kastelein JJ, et al. A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. Arterioscler Thromb Vasc Biol. 2007 Aug;27(8):1803-10.
36. Shafiq N, Bhasin B, Pattanaik S, Pandhi P, Venkateshan SP, Singh M, Malhotra S. A meta-analysis to evaluate the efficacy of statins in children with familial hypercholesterolemia [abstract]. Int J Clin Pharmacol Ther. 2007 Oct; 45(10):548-55.
37. Marais AD, Raal FJ, Stein EA, Rader DJ, Blasetto J, Palmer M, Wilpshaar W. A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia. Atherosclerosis. 2008 Mar;197(1):400-6.
38. Arca M, Montali A, Pigna G, Antonini R, Antonini TM, Luigi P, et al. Comparison of atorvastatin versus fenofibrate in reaching lipid targets and influencing biomarkers of endothelial damage in patients with familial combined hyperlipidemia. Metabolism. 2007 Nov;56(11):1534-41.
39. Lewis JH, Mortensen ME, Zweig S, Fusco MJ, Medoff JR, Belder R, et al. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Hepatology. 2007 Nov;46(5):1453-63.
40. Stein EA, Amerena J, Ballantyne CM, Brice E, Farnier M, Guthrie RM, Harats D, et al. Long-term efficacy and safety of rosuvastatin 40 mg in patients with severe hypercholesterolemia. Am J Cardiol. 2007 Nov 1;100(9):1387-96.

41. Meredith KG, Horne BD, Pearson RR, Maycock CA, Lappe DL, Anderson JL, et al. Comparison of effects of high (80 mg) versus low (20 mg) dose of simvastatin on C-reactive protein and lipoproteins in patients with angiographic evidence of coronary arterial narrowing. Am J Cardiol. 2007 Jan 15;99(2):149-53.
42. Wolffenbuttel BH, Franken AA, Vincent HH. Cholesterol-lowering effects of rosuvastatin compared with atorvastatin in patients with type 2 diabetes: the CORALL study. J Intern Med. 2005 Jun;257(6):531-9.
43. Deedwania PC, Gupta M, Stein M, Ycas J, Gold A. Comparison of rosuvastatin versus atorvastatin in South-Asian patients at risk of coronary heart disease (from the IRIS Trial). Am J Cardiol. 2007 Jun 1;99(11):1538-43.
44. Betteridge DJ, Gibson JM. Effects of rosuvastatin on lipids, lipoproteins and apolipoproteins in the dyslipidaemia of diabetes. Diabet Med. 2007 May;24(5):541-9.
45. Betteridge DJ, Gibson JM, Sager PT. Comparison of effectiveness of rosuvastatin versus atorvastatin on the achievement of combined C-reactive protein (<2 mg/L) and low-density lipoprotein cholesterol (< 70 mg/dl) targets in patients with type 2 diabetes mellitus (from the ANDROMEDA study). Am J Cardiol. 2007 Oct 15;100(8):1245-8.
46. Ferdinand KC, Clark LT, Watson KE, Neal RC, Brown CD, Kong BW, et al. Comparison of efficacy and safety of rosuvastatin versus atorvastatin in African-American patients in a six-week trial. Am J Cardiol. 2006 Jan 15;97(2):229-35.
47. Lloret R, Ycas J, Stein M, Haffner S, et al. Comparison of rosuvastatin versus atorvastatin in Hispanic-Americans with hypercholesterolemia (from the STARSHIP trial). Am J Cardiol. 2006 Sep 15;98(6):768-73.
48. Insull W Jr, Ghali JK, Hassman DR, Y As JW, Gandhi SK, Miller E, et al. Achieving low-density lipoprotein cholesterol goals in high-risk patients in managed care: comparison of rosuvastatin, atorvastatin, and simvastatin in the SOLAR trial. Mayo Clin Proc. 2007 May;82(5):543-50.
49. Leiter LA, Rosenson RS, Stein E, Reckless JP, Schulte KL, Schleman M, et al. Efficacy and safety of rosuvastatin 40 mg versus atorvastatin 80 mg in high-risk patients with hypercholesterolemia: results of the POLARIS study. Atherosclerosis. 2007 Oct;194(2):e154-64.
50. Jones P, Davidson M, Stein E, et al. Comparison of the efficacy and safety of rosuvastatin vs atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). Am J Cardiol. 2003;92:152-60.
51. Stalenhoef A, Ballantyne C, Sarti C, et al. A comparative study with rosuvastatin in subjects with metabolic syndrome: Results of The Comets Study. Eur Heart J. 2005; 1093:822-9.
52. Ballantyne CM, Bertolami M, Hernandez Garcia HR, Nul D, Stein EA, Theroux P, et al. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY (MERCURY) II. Am Heart J. 2006 May;151(5):975.e1-9.
53. Rogers SL, Magliano DJ, Levison DB, Webb K, Clarke PJ, Grobler MP, et al. A dose-specific meta-analysis of lipid changes in randomized controlled trials of atorvastatin and simvastatin. Clin Ther. 2007 Feb;29(2):242-52.
54. Milionis HJ, Rizos E, Kostapanos M, Filippatos TD, Gazi IF, Ganotakis ES, et al. Treating to target patients with primary hyperlipidemia: comparison of the effects of ATOrvastatin and ROSuvastatin (the ATOROS study). Curr Med Res Opin. 2006 Jun;22(6):1123-31.
55. Clearfield MB, Amerena J, Bassand JP, Hernández García HR, Miller SS, Sosef FF, et al. Comparison of the efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia--Prospective study to evaluate the Use of Low doses of the Statins Atorvastatin and Rosuvastatin (PULSAR). Trials. 2006 Dec 21;7:35.
56. Bullano MF, Kamat S, Wertz DA, Borok GM, Gandhi SK, McDonough KL, et al. Effectiveness of rosuvastatin versus atorvastatin in reducing lipid levels and achieving low-density-lipoprotein cholesterol goals in a usual care setting. Am J Health Syst Pharm. 2007 Feb 1;64(3):276-84.
57. Bullano MF, Wertz DA, Yang GW, Kamat S, Borok GM, Gandhi S, et al. Effect of rosuvastatin compared with other statins on lipid levels and National Cholesterol Education Program goal attainment for low-density lipoprotein cholesterol in a usual care setting. Pharmacotherapy. 2006 Apr;26(4):469-78.
58. Ai M, Otokozawa S, Asztalos BF, Nakajima K, Stein E, Jones PH, et al. Effects of maximal doses of atorvastatin versus rosuvastatin on small dense low-density lipoprotein cholesterol level. Am J Cardiol. 2008 Feb 1; 101:315-8.
59. Fox KM, Gandhi SK, Ohsfeldt RL, Blasetto JW, Bays HE. Effectiveness of rosuvastatin in low-density lipoprotein cholesterol lowering and National Cholesterol Education Program Adult Treatment Panel guideline III LDL-C goal attainment compared to other statins among diabetes mellitus patients: a retrospective study using an electronic medical records dataset in the United States. Curr Med Res Opin. 2007 Sep;23(9):2125-33.
60. Harley CR, Gandhi SK, Anoka N, Bullano MF, McKenney JM. Understanding practice patterns and low-density lipoprotein cholesterol goal attainment implications of switching patients from simvastatin in a health plan setting. Am J Manag Care. 2007 Dec;13 Suppl 10:S276-81.

61. Fox KM, Gandhi SK, Ohsfeldt RL, Davidson MH. Comparison of low-density lipoprotein cholesterol reduction after switching patients on other statins to rosuvastatin or simvastatin in a real-world clinical practice setting.Am J Manag Care. 2007 Dec;13 Suppl 10:S270-5.
62. Piorkowski M, Fischer S, Stellbaum C, Jaster M, Martus P, Morguet AJ, et al. Treatment with ezetimibe plus low-dose atorvastatin compared with higher-dose atorvastatin alone: is sufficient cholesterol-lowering enough to inhibit platelets? J Am Coll Cardiol. 2007 Mar 13;49(10):1035-42.
63. Constance C, Westphal S, Chung N, Lund M, McCrary Sisk C, Johnson-Levonas AO, et al. Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared with atorvastatin 20 mg in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2007 Jul;9(4):575-84.
64. Pearson T, Ballantyne C, Sisk C, Shah A, Veltri E, Maccubbin D. Comparison of effects of ezetimibe/simvastatin versus simvastatin versus atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels. Am J Cardiol. 2007 Jun 15;99(12):1706-13.
65. Goldberg RB, Guyton JR, Mazzone T, Weinstock RS, Polis A, Edwards P, et al. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. Mayo Clin Proc. 2006 Dec;81(12):1579-88.
66. Ballantyne CM, Weiss R, Moccetti T, Vogt A, Eber B, Sosef F, et al. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). Am J Cardiol. 2007 Mar 1;99(5):673-80.
67. Ose L, Johnson-Levonas A, Reyes R, Lin J, Shah A, Tribble D, et al. A multi-centre, randomized, double-blind 14-week extension study examining the long-term safety and efficacy profile of the ezetimibe/simvastatin combination tablet. Int J Clin Pract. 2007 Sep;61(9):1469-80.
68. Patel JV, Hughes EA. Efficacy, safety and LDL-C goal attainment of ezetimibe 10 mg-simvastatin 20 mg vs placebo-simvastatin 20 mg in UK-based adults with coronary heart disease and hypercholesterolaemia. Int J Clin Pract. 2006 Aug;60(8):914-21.
69. Chenot F, Montant PF, Marcovitch O, Blaimont M, de Meester A, Descamps OS. Co-administration of ezetimibe and simvastatin in acute myocardial infarction. Eur J Clin Invest. 2007 May;37(5):357-63.
70. McKenney JM, Jones PH, Bays HE, Knopp RH, Kashyap ML, Ruoff GE, et al. Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone (the COMPELL study). Atherosclerosis. 2007 Jun;192(2):432-7.
71. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004 Aug 21-27;364(9435):685-96.
72. Neil HA, DeMicco DA, Luo D, Betteridge DJ, Colhoun HM, Durrington PN, et al. Analysis of efficacy and safety in patients aged 65-75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). Diabetes Care. 2006 Nov;29(11):2378-84.
73. Hitman GA, Colhoun H, Newman C, Szarek M, Betteridge DJ, Durrington PN, et al. Stroke prediction and stroke prevention with atorvastatin in the Collaborative Atorvastatin Diabetes Study (CARDS). Diabet Med. 2007 Dec;24(12):1313-21.
74. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003 Apr 5;361(9364):1149-58.
75. Sever PS, Poulter NR, Dahlöf B, Wedel H, Collins R, Beevers G, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA). Diabetes Care. 2005 May;28(5):1151-7.
76. Winkler K, Ablethauser CB, Gimpelewicz C, Bortolini M, Isaacsohn JL. Risk reduction and tolerability of fluvastatin in patients with the metabolic syndrome: a pooled analysis of thirty clinical trials. Clin Ther. 2007;29:1987-2000.
77. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. JAMA. 1998; 279(20):1615-22.
78. The Pravastatin Multinational Study Group for Cardiac Risk Patients (PMS-CRP). Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dL) plus two additional atherosclerotic risk factors. Am J Cardiol. 1993; 72:1031-7.

79. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care. The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT-LLT). JAMA. 2002; 288(23):2998-3007.
80. Nakamura et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomized controlled study. Lancet. 2006;368:1155-63.
81. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. The West of Scotland Coronary Prevention Study (WOSCOPS). NEJM.1995; 333(20):1301-7.
82. Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM, et al. Long-term follow-up of the West of Scotland Coronary Prevention Study. N Engl J Med. 2007 Oct 11;357(15):1477-86.
83. Asselbergs F., Diercks G., Hillege H., et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation. 2004; Nov 2; 2809-16.
84. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomized placebo-controlled trial. Lancet. 2003;361:2005-16.
85. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg. 2007 Apr;45(4):645-54.
86. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005 Oct 8;366(9493):1267-78.
87. Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008 Jan 12;371(9607):117-25.
88. Pitt B, Waters D, Brown WV, van Boven AJ, Schwartz L, Title LM, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. N Engl J Med. 1999 Jul 8;341(2):70-6.
89. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease End points in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care. 2006 Jul;29(7):1478-85.
90. Schwartz GG, Olsson AG, Szarek M, Sasiela WJ. Relation of characteristics of metabolic syndrome to short-term prognosis and effects of intensive statin therapy after acute coronary syndrome: an analysis of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial. Diabetes Care. 2005 Oct;28(10):2508-13.
91. Olsson AG, Schwartz GG, Szarek M, Luo D, Jamieson MJ. Effects of high-dose atorvastatin in patients > or =65 years of age with acute coronary syndrome (from the myocardial ischemia reduction with aggressive cholesterol lowering [MIRACL] study). Am J Cardiol. 2007 Mar 1;99(5):632-5.
92. Athyros VG, Papageorgiou AA, Mercouris BR, Athyrou VV, Symeonidis AN, Basayannis EO, et al. Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Curr Med Res Opin. 2002;18(4):220-8.
93. Athyros VG, Mikhailidis DP, Liberopoulos EN, Kakafika AI, Karagiannis A, Papageorgiou AA, et al. Effect of statin treatment on renal function and serum uric acid levels and their relation to vascular events in patients with coronary heart disease and metabolic syndrome: a subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) Study. Nephrol Dial Transplant. 2007 Jan;22(1):118-27.
94. Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. Lescol Intervention Prevention Study (LIPS). JAMA. 2002; 287(24):3215-22.
95. Liem A., van Boven A., Veeger N., et al. Effects of fluvastatin on ischemia following acute myocardial infarction: a randomized trial. Eur Heart J. 2002;23:1931-7.
96. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. The Cholesterol and Recurrent Events Trial (CARE). NEJM.1996; 335(14):1001-9.
97. The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. NEJM. 1998; 339(19):1349-57.

98. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. Lancet. 2002; 360:1623-30.
99. Thompson P, Meredith I, Anerena J, et al. Effect of pravastatin compared with placebo initiated within 24 hours of onset of acute myocardial infarction or unstable angina: The Pravastatin in Acute Coronary Treatment (PACT) trial. Am Heart J. 2004;148;1:E1-E8.
100. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). Lancet. 1994;344:1383-9.
101. Chonchol M, Cook T, Kjekshus J, Pedersen TR, Lindenfeld J. Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency. Am J Kidney Dis. 2007 Mar;49(3):373-82.
102. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004 Sep 15;292(11):1307-16.
103. Briel M, Schwartz GG, Thompson PL, de Lemos JA, Blazing MA, van Es GA, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. JAMA. 2006 May 3;295(17):2046-56.
104. Mood GR, Bavry AA, Roukoz H, Bhatt DL. Meta-analysis of the role of statin therapy in reducing myocardial infarction following elective percutaneous coronary intervention. Am J Cardiol. 2007 Sep 15;100(6):919-23.
105. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJ, Eisenberg MJ. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. J Am Coll Cardiol. 2008 Jan 1;51(1):37-45.
106. Bushnell CD, Griffin J, Newby LK, Goldstein LB, Mahaffey KW, Graffagnino CA, et al. Statin use and sex-specific stroke outcomes in patients with vascular disease. Stroke. 2006 Jun;37(6):1427-31.
107. O'Regan C, Wu P, Arora P, Perri D, Mills EJ. Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients. Am J Med. 2008 Jan;121(1):24-33.
108. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005 Apr 7;352(14):1425-35.
109. Waters DD, LaRosa JC, Barter P, Fruchart JC, Gotto AM Jr, Carter R, et al. Effects of high-dose atorvastatin on cerebrovascular events in patients with stable coronary disease in the TNT (treating to new targets) study. J Am Coll Cardiol. 2006 Nov 7;48(9):1793-9.
110. Deedwania P, Barter P, Carmena R, Fruchart JC, Grundy SM, Haffner S, et al. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. Lancet. 2006 Sep 9;368(9539):919-28.
111. Shepherd J, Barter P, Carmena R, Deedwania P, Fruchart JC, Haffner S, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. Diabetes Care. 2006 Jun;29(6):1220-6.
112. Wenger NK, Lewis SJ, Herrington DM, et al. Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. Ann Intern Med. 2007;147(14):1-9.
113. Khush KK, Waters DD, Bittner V, Deedwania PC, Kastelein JJ, Lewis SJ, et al. Effect of high-dose atorvastatin on hospitalizations for heart failure: subgroup analysis of the Treating to New Targets (TNT) study. Circulation. 2007 Feb 6;115(5):576-83.
114. LaRosa JC, Grundy SM, Kastelein JJ, Kostis JB, Greten H, et al. Safety and efficacy of Atorvastatin-induced very low-density lipoprotein cholesterol levels in Patients with coronary heart disease (a post hoc analysis of the treating to new targets [TNT] study). Am J Cardiol. 2007 Sep 1;100(5):747-52.
115. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med. 2007 Sep 27;357(13):1301-10.
116. Shepherd J, Kastelein JJ, Bittner V, Deedwania P, Breazna A, Dobson S, et al. Effect of intensive lipid lowering with atorvastatin on renal function in patients with coronary heart disease: the Treating to New Targets (TNT) study. Clin J Am Soc Nephrol. 2007 Nov;2(6):1131-9.
117. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005 Nov 16;294(19):2437-45.
118. Cannon C, Braunwald E, McCabe C, et al. Intensive vs moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350;15;1495-504.

119. Ray KK, Cannon CP, McCabe CH, Cairns R, Tonkin AM, Sacks FM, et al. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. J Am Coll Cardiol. 2005 Oct 18;46(8):1405-10.
120. Ahmed S, Cannon CP, Murphy SA, Braunwald E. Acute coronary syndromes and diabetes: Is intensive lipid lowering beneficial? Results of the PROVE IT-TIMI 22 trial. Eur Heart J. 2006 Oct;27(19):2323-9.
121. Scirica BM, Morrow DA, Cannon CP, Ray KK, Sabatine MS, Jarolim P, et al. Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. J Am Coll Cardiol. 2006 Jun 6;47(11):2326-31.
122. Ray KK, Bach RG, Cannon CP, Cairns R, Kirtane AJ, Wiviott SD, et al. Benefits of achieving the NCEP optional LDL-C goal among elderly patients with ACS. Eur Heart J. 2006 Oct;27(19):2310-6.
123. Deedwania P, Stone PH, Bairey Merz CN, Cosin-Aguilar J, Koylan N, Luo D, Ouyang P, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). Circulation. 2007 Feb 13;115(6):700-7.
124. Hulten E, Jackson JL, Douglas K, George S, Villines TC. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006 Sep 25;166(17):1814-21.
125. Afilalo J, Majdan AA, Eisenberg MJ. Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials. Heart. 2007 Aug;93(8):914-21.
126. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol. 2006 Aug 1;48(3):438-45.
127. Murphy SA, Cannon CP, Wiviott SD, de Lemos JA, Blazing MA, McCabe CH, et al. Effect of intensive lipid-lowering therapy on mortality after acute coronary syndrome (a patient-level analysis of the Aggrastat to Zocor and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trials). Am J Cardiol. 2007 Oct 1; 100(7):1047-51.
128. Silva MA, Swanson AC, Gandhi PJ, Tataronis GR. Statin-related adverse events: a meta-analysis. Clin Ther. 2006 Jan;28(1):26-35.
129. Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. Circulation. 2006 Dec 19;114(25):2788-97.
130. McClure DL, Valuck RJ, Glanz M, Hokanson JE. Systematic review and meta-analysis of clinically relevant adverse events from HMG CoA reductase inhibitor trials worldwide from 1982 to present. Pharmacoepidemiol Drug Saf. 2007 Feb;16(2):132-43.
131. Newman C, Tsai J, Szarek M, Luo D, Gibson E. Comparative safety of atorvastatin 80 mg versus 10 mg derived from analysis of 49 completed trials in 14,236 patients. Am J Cardiol. 2006 Jan 1;97(1):61-7.
132. Shepherd J, Hunninghake DB, Barter P, McKenney JM, Hutchinson HG. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. Am J Cardiol. 2003 Mar 6;91(5A):11C-7C.
133. Dale KM, White CM, Henyan NN, Kluger J, Coleman CI. Impact of statin dosing intensity on transaminase and creatine kinase. Am J Med. 2007 Aug;120(8):706-12.
134. Silva M, Matthews ML, Jarvis C, Nolan NM, Belliveau P, Malloy M, et al. Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. Clin Ther. 2007 Feb;29(2):253-60.
135. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol. 2006 Apr 17;97(8A):52C-60C.